recent advances in

Obstetrics
and
Gynaecology

J. A. Stallworthy,
F.R.C.S., F.R.C.O.G., Hon.F.A.C.S., Hon.F.C.O.G.(S.A.)

and

eleventh edition

G. L. Bourne,
F.R.C.S., F.R.C.O.G.

RECENT ADVANCES IN OBSTETRICS AND GYNAECOLOGY

11th Edition

The change of editorship of this book is reflected to some degree in the selection of the contents. Apart from the discussion of clinical problems, there is new emphasis on the preventive and social aspects of obstetrics and on the legal problems arising in gynaecological practice. The whole book presents an up-to-date assessment of modern thought in this field of medicine, with notable contributions on "Diabetes" by Sir John Peel, "Anaemia in Pregnancy" by Dr. Louis Steingold and "Applications of Chromosome Studies in Obstetrics and Gynaecology" by Dr. Alan Stevenson.

60s.

RECENT ADVANCES
IN OBSTETRICS
AND GYNÆCOLOGY

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AND GYNÆCOLOGY

ELEVENTH EDITION

by

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With 73 illustrations

J. & A. CHURCHILL LTD.,
104 Gloucester Place, London, W.1.
1966

First Edition	1926
Second Edition	1928
Third Edition	1932
Fourth Edition	1939
Fifth Edition	1942
Sixth Edition	1945
Reprinted	1946
Seventh Edition	1948
Eighth Edition	1953
Ninth Edition	1958
Tenth Edition	1962
Eleventh Edition	1966

H. 11-1-67

AN APPRECIATION

Many who will read this book were not born when the first edition was published in 1926. The author, Mr. Aleck Bourne, was a young consultant on the staff of St. Mary's and the Samaritan Hospitals London, but was already well known to English speaking students throughout the Empire, as it then was, because of his popular and brilliant little *Synopsis of Obstetrics and Gynæcology*. For the next 36 years Mr. Bourne, joined later in 1932 by Mr. Leslie Williams, recorded faithfully and critically in ten editions advances in Obstetrics and Gynæcology. This book together with their many other contributions established for them an international reputation as teachers and leaders in British Medicine.

In the Preface to the tenth edition, published in 1962, they stated "we, the authors, take the bow at the curtain as it descends after so many years." The scene is one of triumph as well as of sadness. The task and privilege of preparing this new edition of a now famous book has been entrusted to us by Mr. Bourne. We take over where he and Mr. Williams left off, and as the curtain falls and they take their bow we would wish to begin our new role by leading the well merited applause.

J. S.
G. B.

PREFACE

The curative property of certain moulds was known long before penicillin was discovered by Fleming and established as a therapeutic agent by Florey. In Medicine recent advances are often no more than a consolidation of facts long since recorded but now seen with new implications. It is inevitable that subjects which have been discussed already will be reviewed from time to time in a book such as this. The central theme of this edition is "The Avoidable Factor".

The new authors hope to maintain the tradition established by their predecessors to emphasize developments which have led to advances in Obstetrics and Gynæcology, or give promise of doing so. Ideas and concepts of organization as well as details of technique have been appraised. Realization that accepted methods are not yielding the results at first expected can be the first stage of a major advance, and criticism when merited is good for the soul.

One of us (G.B.), like his predecessors, is on the staff of a famous London teaching hospital. The fact that he shares the same distinguished name as the original author is a coincidence. The other (J.S.) learns and teaches in a large postgraduate medical centre with a small graduate medical school at Oxford. These London and Oxford appointments give contact with specialists and specialists in training from many parts of the world and bring a constant awareness that clinical problems which may be common in one place are seldom seen in another.

We are deeply indebted to Sir John Peel for his contribution on Diabetes, to Dr. Louis Steingold for his chapter on Anæmia in Pregnancy and to Dr. Alan Stevenson for his review of the rapidly expanding field of Chromosome Studies. These important chapters have been written by three outstanding experts.

The Editors are grateful to colleagues who have kindly supplied illustrations, and to editors and publishers for permission to reproduce them. Some of them are acknowledged where they appear; others are as follows: American Journal of Obstetrics and Gynecology for Figs. 16, 17; Annals of the Royal College of Surgeons of England for Fig. 62; British Medical Journal for Figs. 57, 65;

Fertility and Sterility for Figs. 51, 55; Lloyd-Luke (Medical Books) Ltd. for Figs. 18–36.

Messrs. J. & A. Churchill have been both tolerant and patient with the new team of authors, and we in turn are grateful, especially to Mr. Rivers for his guidance and cooperation.

J. S.
G. B.

CONTENTS

MATERNAL MORTALITY
WITH
A REVIEW OF CONTEMPORARY OBSTETRICS

Antenatal Care and Maternal Mortality were the subjects chosen for the two opening chapters of the first edition of "Recent Advances in Obstetrics and Gynæcology" published in 1926. Mr. Aleck Bourne began the series with the words:

"It is only of recent years that Obstetrics has been recognized as a branch of preventative medicine, . . . This attitude towards obstetrics, first of the profession and now of the public, is thoroughly justified in view of the immense amount of ill-health and disability which can be prevented by antenatal supervision and the proper conduct of labour."

It is appropriate that 40 years later new authors should begin their first edition with reference to these same subjects. Both are dealt with in the one chapter as a deliberate attempt to emphasize an integration of practice which has been responsible for recent advances in Obstetrics and Gynæcology.

There are two reasons why this choice of opening subject is appropriate. The first is to pay tribute to the vision Mr. Bourne shared with others of the role of antenatal care in preventive medicine. Their views were a challenge to obstetric thought in the mid-twenties. The expanding concept of what now constitutes adequate care is a significant advance with an effect on obstetrics and pædiatrics that is already considerable and will continue. The second reason is that the recent history of maternal mortality in Britain is a record of great achievement, the implications of which have not been appreciated as widely as they deserve.

The idea which was translated into a successful attempt to reduce maternal mortality in England and Wales could be applied just as readily in other fields of medicine. It could improve the prognosis of uterine cancer, reduce the complications of tonsillectomy, lower the mortality from road accidents, or clarify the medical treatment of urinary infections. It consisted of analysing on a national scale the

circumstances leading up to every maternal death and from accumulated evidence advising on how to avoid repeating the same mistakes, and was so successful that no apology is offered for giving a brief resumé of the historical background.

History

In 1926 when the first edition of "Recent Advances" was published, the maternal mortality rate had shown little variation from approximately 4 per 1,000 since 1900. It varied from 4·27 in 1901–05 to 3·55 in 1918. In 1929, when the Royal College of Obstetricians and Gynæcologists was incorporated, it was 4·16, including abortion deaths. In 1928, when the rate was 4·4 and approximately 1,000 women died every year from puerperal infection, the Minister of Health was a man who will be remembered for his role at Munich rather than for his contribution to obstetrics. He was Mr. Neville Chamberlain. There were 660,267 live births in England and Wales with 2,920 maternal deaths that year. Because of public concern Mr. Chamberlain appointed a Departmental Committee to advise on Maternal Mortality and Morbidity. Two years later it introduced the concept of a "Primary Avoidable Factor" which was defined as a departure from accepted standards of satisfactory care from which ensued the train of events resulting in death. This definition was not static in its implications but provided a reasonable though changing yardstick with which to assess standards of care. Certain aspects of obstetric supervision considered satisfactory in 1932 would be regarded as highly unsatisfactory in 1965 as described later. An avoidable factor was detected in 45·9% of 5,800 deaths.

Maternal mortality was discussed at the 12th British Congress of Obstetrics in 1949 and a technique of enquiry used in the United States was described. It consisted of the investigation of maternal deaths by a committee of local experts. Sir Eardley Holland, President of the Congress, suggested to the Minister of Health that the American method could possibly be adopted with benefit in Britain. Consultations followed between the Royal College of Obstetricians and Gynæcologists and the Society of Medical Officers of Health and a new system of enquiry began in 1952. It maintained the original confidential nature of the 1928 enquiry but planned to integrate all who could contribute information and was based on the voluntary participation of doctors or midwives who had the misfortune to be associated with a maternal death.

Enquiry Procedure

The enquiry into each death is confidential and information is recorded on a standard form issued by the Ministry. This document is marked "STRICTLY CONFIDENTIAL, For Medical Use Only", and headed "Report on Death due to, or associated with, Pregnancy, Childbirth or Abortion". Deaths associated with pregnancy are classified by the Registrar-General under two separate headings commonly referred to as Maternal Deaths and Associated Deaths. They can be defined as follows:

Maternal Deaths

These are due to complications of pregnancy, labour and the puerperium.

Associated Deaths

These are due to disease, violence or accident involving the death of a pregnant woman, but are not the result of pregnancy, labour or the puerperium.

Note.—The causes of Associated Deaths as listed by the Registrar-General are summarized in Table 1.

Maternal Mortality

This is the incidence of maternal deaths expressed, unless otherwise stated, as the number per 1,000 total births (live and still-births).

Note 1.—Now that the figure for England and Wales is so low (0·28 is the Registrar-General's provisional figure for 1963) maternal mortality is sometimes expressed as the number per 10,000 births, e.g. 2·8 per 10,000 total births.

Note 2.—Unless otherwise stated, maternal mortality includes deaths from abortion and ectopic pregnancy. The contribution these make to the total is shown in Tables 2 and 3.

In the years reviewed in Table 2 ectopic pregnancy and abortion accounted for 15–21 % of the total deaths, a higher proportion than is generally recognized. The number dying from both these causes has fallen considerably since 1952 (Table 3). To make the records complete it is necessary for all deaths occurring within a year of termination of pregnancy to be notified. This fact, together with study of the causes of Associated Deaths summarized in Table 1, emphasizes two points of practical importance.

Table 1
ASSOCIATED DEATHS.

("Deaths not classed to Pregnancy & Childbirth but associated therewith")

CAUSE OF DEATH

SUMMARY:

INFECTIOUS and PARASITIC DISEASES
NEOPLASMS
ALLERGIC and METABOLIC DISEASES
DISEASES of BLOOD and BLOOD-FORMING ORGANS
MENTAL, PSYCHO-NEUROTIC and PERSONALITY DISORDERS
DISEASES of NERVOUS SYSTEM
DISEASES of CIRCULATORY SYSTEM
DISEASES of RESPIRATORY SYSTEM
DISEASES of DIGESTIVE SYSTEM
DISEASES of GENITO-URINARY SYSTEM
DISEASES of BONES and ORGANS of MOVEMENT
CONGENITAL MALFORMATIONS
SYMPTOMS, SENILITY, and ILL-DEFINED CONDITIONS
ACCIDENTS, POISONING and VIOLENCE.

Table 2
MORTALITY RATE FOR ENGLAND & WALES
1950 − 1963
Registrar General's Review.

	1950	1955	1960	1963
MATERNAL MORTALITY	0.87	0.59	0.39	0.28
MM. (Excluding ECTOPIC PREGNANCY & ABORTION)	0.72	0.5	0.31	0.22

Table 3
DEATHS DUE TO ECTOPIC PREGNANCY & ABORTION

Registrar General's Review.

	1952-54	1955-57	1958-60
ECTOPIC PREGNANCY	78	62	42
ABORTION	242	199	172

The first is that it may be difficult to decide whether a death should be classified as a "Maternal" or an "Associated Death", as when a patient with heart disease dies from the cardiac lesion during Cæsarean section. The second point is that while most women who die many months after childbirth do so because of reasons not associated with pregnancy, in others there is a causal relationship. An example is death from chorion epithelioma. Unless all are investigated some will be missed. If all are notified some will be rejected from the Enquiry statistics, as for example when they occur in accidents, but the rejection matters little and will have the advantage of being made by one experienced team instead of depending on the differing views of many doctors directly associated with the patients concerned.
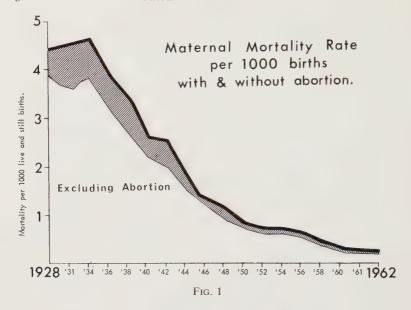
The practical implication is that there are four circumstances under which a practitioner, having signed the statutory death certificate, should initiate the Enquiry by obtaining the requisite form from the local Medical Officer of Health. They are:

1. If the patient died as the result of pregnancy, labour or the puerperium.
2. If death was due to associated causes.
3. If death occurred within a year of delivery or abortion and was due to complications arising from or associated with the pregnancy.
4. If there is doubt on whether a death should be included in the Enquiry or not.

Results

This experiment, conceived and conducted on a grand scale, has within a few years yielded dramatic results, not least of which is a lowering of maternal mortality from 0·87 in 1950 to 0·28 in 1963, a reduction to one-third of the 1950 figure. This occurred when no new discovery could explain the sudden improvement, as happened in 1936 with Colebrook's work on droplet infection followed by sulpha drugs and antibiotics, the impact of which is revealed in Fig. 1. When the present Enquiry began the toll of death from all causes was approximately half of that caused by infection alone when the Committee published its first report in 1930. In spite of this the record low rate of 0·28 was achieved (0·22 excluding deaths from ectopic pregnancy and abortion).

Midwives, general practitioners and specialists assist in the Enquiry on a voluntary basis, and the fact that in the three years

Fig. 1

1958–60 80% of maternal deaths (742 of 928) were notified, indicates the extent of co-operation. Sometimes a case history makes it clear that there are grounds for criticism. None is offered. In providing the required information those clinically associated with the patient have an opportunity of reviewing the circumstances of the tragedy and discussing them with colleagues. This enables a clinician to appraise his own work and to profit from mistakes.

The success of the Enquiry depends on four points:

1. The necessity of having one person responsible for it in each area.
2. The compilation of accurate information.
3. A critical assessment of avoidable factors.
4. A mechanism by which any action found to be necessary can be taken.

The local Medical Officer of Health occupies a key position. He initiates or takes an active part in every enquiry in his area and from the information received is briefed to take any administrative action necessary. For example, where there was no emergency obstetric service this fact was emphasized if patients died in transit to hospital. He was thus in a strong position from which to exert the

pressure necessary to establish an effective Flying Squad service. If the Enquiry revealed that a Flying Squad with a junior medical officer in charge was not able to cope with a desperate emergency the adequate staffing of the service became an administrative matter.

The compilation of information is the responsibility of a regional consultant who is a member of the Central Committee of the Ministry of Health. Success depends on accurate and detailed records. To say that all necessary facilities were available to deal with an emergency does not necessarily mean that they were used. When they are not the tragedy of a maternal death is even more poignant. An important side effect of the Enquiry has been an improvement in the standard of records. Whereas in the first two Reports (Walker *et al.*, 1957, 1960) deaths were classified as unavoidable when insufficient information was given to enable the assessors to determine exactly what happened, in the last one (1963) this was not necessary. In an age in which computers are revealing exciting glimpses of their future contribution to medical progress this emphasis on accurate recording may provide a pattern for other important experiments on a national or international scale.

This is illustrated by comparing records from the Registrar-General with those of the Enquiry for the same period. Doctors who signed the death certificates were those who provided the necessary information for the Enquiry. From 1952–60 the Registrar-General classified 236 deaths as due to "puerperal phlebitis and thrombosis" (Table 4), whereas detailed study of these resulted in the inclusion of only 2 under this heading. The Registrar-General attributed "puerperal pulmonary embolism" as the cause of death in only 131 patients, whereas details available to the Ministry enabled them to include 386 patients in this group (Table 5).

Table 4

PUERPERAL PHLEBITIS & THROMBOSIS.

YEARS	REGISTRAR GENERAL	ENQUIRY
1952 1953 1954	92	0
1955 1956 1957	83	0
1958 1959 1960	61	2
TOTALS	236	2

Table 5

PUERPERAL PULMONARY EMBOLISM.

YEARS	REGISTRAR GENERAL	ENQUIRY
1952 1953 1954	59	138
1955 1956 1957	36	147
1958 1959 1960	36	101
TOTALS	131	386

The regional assessor may take steps to obtain further details. For example, certified cause of death may be postpartum hæmorrhage, but if labour was induced by oxytocic infusion after intra-uterine fœtal death and was rapid, the assessor would suspect that the hæmorrhage was a manifestation of amniotic embolism with fibrinogen depletion. He would ask for further information on the autopsy findings and the histology of the lungs. If this confirmed the diagnosis the certified cause of death would be altered for the Enquiry records. On the completed document he discusses avoidable factors which may relate to the patient, relatives, doctor, or midwife; reviews the administrative aspects of the case and states whether in his opinion death was avoidable or unavoidable. If there is doubt he says so. The completed document is sent to the Ministry of Health where the two senior advisers, Sir Arnold Walker and Mr. A. J. Wrigley, co-ordinate the records, make the final assessments, and play a major part in preparing the Reports on Confidential Enquiries into Maternal Deaths published by the Stationery Office (Nos. 97, 103, and 108). A fourth has been published in 1966 as Report No. 115.

These Reports record a progressive reduction in the number of maternal deaths, indicate ways in which improvements can be achieved, and analyse critically the avoidable factors. The purpose of the Enquiry was restated in the preface to the 1963 Report:

It is well to be clear as to the object of the exercise. . . . to try to identify those factors which could be regarded as avoidable. This does not necessarily mean that a factor so identified was the cause of the mother's death. It does mean that if the avoidable factor or factors had been recognized or anticipated and handled in accordance with the best current practice a fatal issue might have been avoided.

Avoidable factors were identified in 42% of maternal deaths 1952–60 (Table 6) and in 17% of associated deaths (Table 7). Maternal mortality is now at a level which would have been considered impossible 30 years ago and improbable even 10 years ago, but avoidable factors in 42% of deaths constitute a major challenge. If the standards of obstetric care were uniformly in accordance with

Table 6

AVOIDABLE FACTORS, 1952–60.

	No. with Avoidable Factors	Maternal Deaths
1952–54	472	1094
1955–57	353	861
1958–60	315	742
	1140 (42%)	2697

Table 7

AVOIDABLE FACTORS, 1952–60.

	No. with Avoidable Factors	Associated Deaths
1952–54	53	316
1955–57	57	339
1958–60	45	254
	155 (17%)	909

the best current practice the rate might be almost halved to reach 1·6 per 10,000 births. Moreover, if departures from accepted practice are associated with over 40% of maternal deaths they certainly exist in the care of many women who survive. The work of Acheson *et al.* (1964) on record linkage emphasizes this point. For example, in a region with the lowest maternal mortality in Britain, 43% of patients at high risk such as grandmultiparæ were booked for general practitioner care.

The four main causes of maternal death throughout the Enquiry were:

1. Toxæmia.
2. Hæmorrhage.
3. Abortion.
4. Pulmonary embolism.

Their incidence in the first 3 years (1952–54) is given in Table 8.

Table 8

MAIN CAUSES OF MATERNAL DEATH

1952–54

TOXAEMIA	246	22%
HAEMORRHAGE	188	17%
ABORTION	153	14%
EMBOLISM	138	13%

Note :

This Table refers only to deaths notified
and investigated in the Enquiry. In the years
under review (1952–54) these accounted for
78% of the total maternal deaths (1094 in 1403),
but Toxaemia and Haemorrhage in that order
were also the main causes of death in the
Registrar General's total figures.

Nomenclature used in classification has affected the totals ascribed to each category but since a standard pattern has been adopted trends are accurately recorded. For example, many women dying of abortion perish from hæmorrhage but the death is classified under abortion. Others who die from blood loss during operation are included under Cæsarean section. This means that deaths included under hæmorrhage represent the minimum for which this complication is responsible, but it also means that relevant avoidable factors have a wider application than is at first apparent.

These four complications were responsible for approximately 70% of all deaths. Table 9 demonstrates a progressive fall in the total number, and the relative importance of each complication until in 1958–60 toxæmia, abortion and pulmonary embolism were

Table 9

MAIN CAUSES OF MATERNAL DEATH

	1952-54 No. %	1955-57 No. %	1958-60 No. %
TOXAEMIA	246 22%	188 22%	137 18%
HAEMORRHAGE	188 17%	121 14%	114 15%
ABORTION	153 14%	141 16%	135 18%
EMBOLISM	138 13%	147 17%	132 18%
TOTALS	725	597	518

equal (18% each), while hæmorrhage fell to fourth place (15%). The reduction was more gratifying because the number of births rose by 13% from 2,052,000 in 1952–54 to 2,322,229 in 1958–60. In spite of this the number of deaths due to these four causes fell from 725 in 1952–54 to 518 in 1958–60, a reduction of 28%.

The total material analysed consisted of 2,697 maternal deaths and 909 associated deaths representing 87% of 3,444 maternal deaths and 88% of 1,032 associated deaths in 6,532,625 deliveries. These would have been associated with 28,700 maternal deaths had the mortality remained at the 1928 figure of 4·4.

When for the first recorded time in history an athlete runs a hundred yards in 10 seconds, or a mile in under 4 minutes, general admiration for the achievement is inevitably mingled with the question of whether it will be humanly possible to lower the record much further. Time shows that it is. The higher the standard the greater the effort to improve it. The fact of this dramatic improvement in obstetric results demands a closer study of how it was accomplished if there is to be a reasonable prospect of continued progress.

The first Report (Walker *et al.*, 1957) was a pilot survey of the problem. It analysed the main causes of death and reviewed the avoidable factors, indicating ways both administrative and clinical by which improvements could be made. It emphasized that medical and obstetric care should be in accordance with the "best current practice" and gave guidance on what this should be. None of the Reports suggested therapeutic techniques. These were not in their terms of reference but they stressed the need for a wider use of knowledge already available with the corollary, tragically illustrated, that departure from these standards carried unjustifiable risks.

Education was necessary so that ignorance should not lead to repetition of past errors. The Reports were available for 3/6, 4/– and 4/6 respectively, but were supplied to Regional Boards and Boards of Governors which in some cases at least forwarded them to Obstetric Advisory Committees for detailed study and recommendations. A brief summary emphasizing practical points was sent to every doctor practising obstetrics in some areas and the advisability of supplying one to all practitioners engaged in obstetrics is under review by the Central Health Services Council (1964).

Lectures on lessons to be learned from the Enquiry are given in some Medical Schools and can be valuable and exciting. The medical press gave fair publicity to the Reports in editorials and annotations, and sections of the lay press drew attention to them, though not always with impartial appraisal of the revolution which was being enacted to the benefit of patients. Sensational headlines highlighting the occasional tragedy were unworthy and showed no appreciation of the fact that in no other branch of medicine was the process of voluntary collaboration used with such outstanding results. Possible medico-legal repercussions of this type of publicity are discussed in Chapter 9.

The technique used in the Enquiry and the widespread co-operation it received have been major advances in obstetrics. "Avoidable factors" and the "best current practice", together with recent advances of importance, will now be considered.

Avoidable Factors

Definition:

An avoidable factor is a departure from the best current clinical practice preceding a maternal death, but not necessarily responsible for it.

In the Enquiry "avoidable factor" is always used in association with maternal deaths, whereas in practice departures from generally accepted routines are fortunately seldom followed by tragedy. Nonetheless, recognition of their dangers is a major contribution. They can be grouped under four main headings with an incidence summarized in Tables 6 and 7.

1. The patient's attitude.
2. Inadequate antenatal care.
3. Confusion of responsibility.
4. Inadequate intrapartum and postpartum care.

Sometimes there are multiple factors.

1. The Patient's Attitude

In over six and a half million consecutive deliveries 308 toxæmic deaths had avoidable factors and in 76 (25%) the patient failed to accept medical advice. Her attitude was often encouraged by relatives. Some women conceal their pregnancies. Some do not keep appointments, while others refuse admission to hospital when it is advised. The result is that some are found dead at home or are admitted to hospital *in extremis*. The patient's attitude was also an avoidable factor in deaths from causes other than toxæmia and most women in this group were multigravidæ. A gravida 5 is at greater risk than a primigravida and increasing parity adds to her danger. It is easy to understand why a woman who has been delivered safely at home should object to subsequent hospital delivery and both tact and firmness may be necessary to persuade her. Many mothers have perished because of failure to take this advice. Patient attitude was the avoidable factor in 26% of all maternal deaths in the years 1958–60, although no section of the Obstetric Service was free from responsibility (Table 10).

Table 10

AVOIDABLE FACTORS, 1958-60

Distribution

Responsible Person	No.	%
GENERAL PRACTITIONER	136	39%
PATIENT or RELATIVE	91	26%
CONSULTANT or SPECIALIST in TRAINING	85	25%
MIDWIFE	19	5.5%
LOCAL AUTHORITY MEDICAL OFFICER	12	3.5%
UNSPECIFIED	4	1%

2. Inadequate Antenatal Care

Patients who fail to keep antenatal appointments may be over-looked and the organization needs to be good to avoid this. When the dangers were recognized the Ministry requested hospitals to review appointment systems so that steps could be taken to find the reason why a patient failed to attend. Those who are apparently indifferent to the danger of not accepting advice on these matters

present a challenge to the obstetric, health, and education services. These must accept responsibility for educating the public It is essential to gain the confidence of a pregnant woman and to guide and at times lead her when folly threatens disaster.

Defect of antenatal care was associated with 180 deaths in the years 1958–60. This was 57% of the 315 deaths with avoidable factors and 24% of the total of 742. Similar errors of omission and commission recurred in both domiciliary and hospital practice and can be summarised as follows:

    A. Booking potentially abnormal patients for delivery at home or in general practitioner units.
    B. Failure to assess the patient's general health.
    C. Failure to make hæmoglobin estimations and other necessary tests.
    D. Failure to recognize signs of impending trouble.
    E. Failure to act when signs are detected.

Experience has long since established that efficient antenatal care is preventive medicine at its best. Originally designed for the abnormal patient its contribution to supervising the normal was appreciated. In obstetrics the apparently normal is the potentially abnormal and the change can occur with frightening rapidity, but there is often evidence by which to select patients at greatest risk before an emergency arises. This demands eyes trained to see, hands skilled to feel, and a brain disciplined to co-ordinate and act. Failure to appreciate these points has been the basis of most defects in antenatal care.

Home or Hospital Confinement?

Signing a death certificate can begin by booking unwisely for home delivery those at increased risk (Fig. 2). The grand multipara is particularly at hazard and accounts for over one-fifth of all deaths from hæmorrhage, and over one-third from placenta prævia. Only 4·2% of multiparous women develop toxæmia compared with 8·5% of primigravidæ, but the incidence in a multipara with a history of toxæmia rises to 31·7% and the risk of death increases after the fourth pregnancy (Gemmell *et al.*, 1954). In all toxæmia deaths the proportion of gravida 5 and more is $2\frac{1}{2}$ times greater than for all legitimate births, yet these are patients by whom considerable pressure may be exerted to have a home delivery. It is no kindness but highly dangerous to agree. Delivery in hospital and early transfer home can be a satisfactory compromise.

HIGH RISK PATIENTS UNSUITABLE FOR HOME DELIVERY

MATERNAL MORTALITY

1.
ASSOCIATED ILLNESS:-
        CARDIO-VASCULAR,
        DIABETES, C.N.S.

        ≈ ≈

2. GRAND MULTIPARA (GRAVID 5+) BEWARE 9 + !

        ≈ ≈

3. PREVIOUS OBSTETRIC COMPLICATIONS
        TOXAEMIA, DYSTOCIA, P.P.H.

        ≈ ≈

4.
MULTIPLE PREGNANCY

        ≈ ≈

5.
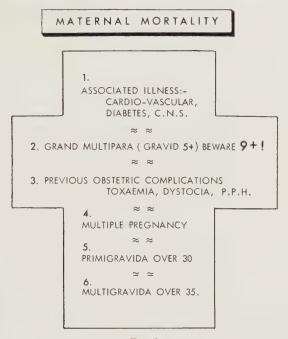PRIMIGRAVIDA OVER 30

        ≈ ≈

6.
MULTIGRAVIDA OVER 35.

Fig. 2

Just as a history of toxæmia increases the risk, so hæmorrhage, both antepartum and postpartum, tends to recur in subsequent pregnancies. Both are a warning against home confinement.

A multigravida with a bad obstetric history was booked for home confinement. When toxæmia developed she was told to rest and a fortnight later was admitted to hospital a few hours before she died of toxæmia and anæmia. Her hæmoglobin was then 38%.

A patient with multiple pregnancy is undoubtedly fascinating. Because a doctor has delivered one or two women safely at home with twins he should not neglect the warning that these patients and their infants are threatened by many complications which include toxæmia, hæmorrhage, prematurity, malpresentation and intra-uterine asphyxia. Closer supervision than usual is necessary and should be a consultant responsibility. Safe delivery requires hospital facilities.

A multigravida 6 aged 42 was booked for home confinement. It was known that she had heart disease. Late in pregnancy twins were diagnosed. She complained of extreme tiredness and was advised to rest. She went into premature labour and died undelivered from acute cardiac failure. Consultant advice was not requested on either the obstetric position or the heart lesion.

Four contra-indications to home delivery were ignored:

1. Heart disease.
2. Gravida 6.
3. Multiple pregnancy.
4. The age of 42.

One lesson taught by the many tragedies recorded in the Reports concerns the term "safely delivered". Much depends on the point of view. When an acrobat with skill and daring walks across Niagara Falls on a tightrope the Press may comment on his safe crossing, whereas many would consider that he crossed dangerously. Because a doctor practises midwifery for a considerable time without a maternal death it does not follow that he is a safe obstetrician. Conversely, if he has a maternal death his skill or the care he has shown are not necessarily in question, but if he uses methods which experience has demonstrated to be dangerous he is not practising safely. The completion of a task is not proof that the method used is free from criticism. If it is, one can expect consistently good results from its continued use, but if it is not and includes an element of danger, tragedy is likely to follow sooner or later for the same reason that a driver is killed when crossing the double white lines after gaining false confidence from never having had an accident.

Inadequate Attention to General Health

Neglect of the medical aspects of antenatal care contributed many avoidable factors. Emphasis on the mechanics of obstetrics seemed on occasions to divert attention from the patient's general health. The quality rather than the quantity of antenatal care was sometimes at fault. Frequent recording of uterine sizes and fœtal positions would include no reference to hæmoglobin estimation, rhesus grouping, Wassermann or Kahn reactions, or to associated medical diseases. Cardiac murmurs or irregularities would be detected without requesting an expert assessment. Even in 1958–60 hæmoglobin levels were recorded in only 48% of 130 patients who died from hæmorrhage, and in 36·9% of all maternal deaths.

There is world-wide evidence of the increase of syphilis. The serious medical and medico-legal implications (Chapter 9) of not

detecting this disease in time to avoid the disaster of congenital infection needs emphasis. Woody *et al.* (1964) reported an increased incidence of florid congenital syphilis, whereas adequate treatment before the last month of pregnancy reduces the risk to less than 2 %. Generations of doctors relatively unfamiliar with clinical syphilis are responsible for delay in diagnosis even when such symptoms as persistent napkin rash, broncho-pneumonia and intractable rhinitis with mucopurulent discharge should arouse suspicion.

Errors of omission and commision were not confined to rare conditions. Common complications such as toxæmia and anæmia were frequently associated with avoidable factors. Rising blood pressure, excessive gains in weight and albuminuria were recorded without action being taken.

A primigravida aged 39, booked for home confinement, gained 42 lb. (18·9 kg.) in 11 weeks, developed massive œdema, a pressure of 180/100, but was kept at home. She died of toxæmia.

Antenatal care makes its greatest contribution only when it promotes the necessary informed action. The detection of trouble has no merit unless necessary steps are taken to deal with it. When relevant avoidable factors were unknown, chances were taken sometimes in ignorance, but the Enquiry has altered this and they should now be recognized by all who practise obstetrics.

Walker *et al.* (1957) emphasized that *the first antenatal consideration* should be an assessment of general health. Most reports at that time gave little information on this point. The importance of personal history and environment in relation to pregnancy, as well as nutritional state and general health, both physical and emotional, was stressed.

The emotional aspect of pregnancy and labour is of great importance to most women, and the profession cannot afford to ignore it. In its simple form the desire of a wife to have her husband share with greater understanding the changes through which she passes, is likely, if granted, to lead to a higher standard of antenatal and intrapartum care as well as to their mutual happiness. Their interest will result in explanations being given and a tutorial often instructs the tutor as much as the pupil.

Natural Childbirth

It is not incongruous to refer to this when dealing with maternal mortality. Some exponents of natural childbirth overlook the fact in reference to the obstetric performance of primitive people that

this is associated with a high mortality and morbidity. Because of the major role inadequate antenatal care plays in relation to maternal deaths, it follows that any measure which can raise the standard of care should be encouraged.

Grantly Dick Read (1950) attracted a considerable following with his views on natural childbirth. There are many modifications of the general theme, including the Russian summarized by Nikolayev (1964), and the French (Vellay, 1964), and the American (Lee Buxton, 1962). The literature now includes papers from most countries and those interested will find a useful bibliography in the *Journal of the International Federation of Gynæcology and Obstetrics*, 1964, No. 1, Volume 2. In the meantime, it is sufficient to record that although interest in this aspect of obstetrics is gaining momentum the extent of its contribution has yet to be assessed. One fact is certain, that it is as impossible to convert obstructed labour into natural childbirth as to make a silk purse from a sow's ear. When the obstetric position is unfavourable, normal delivery may be an impossibility. This indicates that in relation to a patient's emotional health antenatal errors can be made in two main ways. The more common neglects emotional aspects while concentrating on the mechanics of obstetrics while the other, which will become increasingly important and can be dangerous, is to concentrate on the emotional preparation and pay insufficient attention to obstetric factors. This applies particularly to the choice of home as the place of delivery for high risk patients (Fig. 2), and introduces avoidable factors. However well the patient is prepared emotionally and however confident she may feel these factors still operate.

A primigravida aged 40, wife of a university don, had been an infertility problem successfully treated by multiple myomectomy. Both patient and husband were keenly interested in natural childbirth and attended classes of instruction. At the 38th week the patient decided to cancel her hospital booking and have the baby at home. Not until she and her husband were informed that this would amount almost to culpable negligence were they persuaded to continue with the original plans.

When 9 days overdue she was in hospital in vague labour, but at 11 p.m. dressed and without speaking to nurse or doctor was leaving hospital when intercepted by a Registrar. In spite of his protests she went home and returned at 2 a.m. with ruptured membranes, in pain, and with an irregular fœtal heart rate of 80. Oxygen and immediate section resulted in the delivery of a living son.

This irresponsible behaviour by an intelligent woman indoctrinated with the concept of natural childbirth adds weight to the warning given above.

3. Confusion of Responsibility

With efficient antenatal care the right choice of place of delivery would be made and no confusion of responsibility could arise during pregnancy. When this standard becomes "current practice" the maternal mortality rate should be at a minimum, probably of the order of 1 per 10,000. Until then there are practical advantages in dealing with these issues separately because of their causal relationship to many avoidable deaths. For example, in the 1963 Report 180 deaths were associated with avoidable factors confined entirely to the antenatal period, and in 18 an obstetrician was involved because of confusion of responsibility. Women were booked for hospital delivery but lapses in antenatal care included failure to recognize defaulting from clinics and the neglect of anæmia and early signs of complications, when antenatal care was shared between hospital, general practitioner, and midwife. For this reason the doctor who books a patient for delivery must accept responsibility for her. If he delegates part of the antenatal care to a colleague, he must know that it will be performed effectively and that he is notified of impending trouble. Confusion of responsibility caused the death of 17 toxæmic patients in the years 1955–60.

In spite of examples of inadequate care, obstetric standards in England and Wales improved progressively during the Enquiry. The number of deaths due to toxæmia and hæmorrhage fell by 42% from 434 in 1952–54 to 251 in 1958–60, the more encouraging because of a 13% rise in the number of births. The reduced mortality from hæmorrhage, as discussed later, is largely due to better intrapartum and postpartum care, whereas improved toxæmia results follow more efficient antenatal care.

Toxæmia

The statement that no major improvement could be expected in toxæmia results until its ætiology and pathology were better understood has proved an acceptable preface to many applications for research funds. The need for research remains. The contemporary position was summarized in a *British Medical Journal* leading article (1964, p. 459), but the Enquiry has demonstrated what the clinician can do to reduce the lethal potential of this complication. Death from toxæmia of pregnancy may soon be considered almost entirely preventable, although fulminating cases, rare in Britain, but more common in some parts of the world, will continue to

defeat the most conscientious antenatal supervision. Deaths from toxæmia alone fell by 44% from 246 in 1952–54 to 137 in 1958–60 (Table 9). Avoidable factors rose from 52% to 56%, suggesting that the mortality could be halved if the "best current practice" were adopted consistently.

Toxæmia deaths (1952–60) numbered 571 of which 308 (54%) had avoidable factors. Failure of the patient to co-operate (25%) and delivery in unsuitable places (83% in 1952–54 and 78% in 1958–60) were recurring problems. These facts indicate the path of future progress. Avoidable factors have now been defined clearly with particular reference to those patients at increased risk and defects in antenatal care. The best current practice takes cognizance of these warnings.

4. Inadequate Intrapartum and Postpartum Care

Excluding deaths from abortion in the years 1955–60 there were 478 maternal deaths and 102 associated deaths with avoidable factors, a total of 580. In 35% (203) care during delivery or in the puerperium was at fault. The fact that 65% of mistakes were in antenatal care gives perspective which is easy to forget when reviewing the drama of hæmorrhage, shock or embolism.

Important avoidable factors are illustrated by the recent progress made in the treatment of obstetric hæmorrhage. Some improvement is due to a wider acceptance of the "best standards of practice" and some to the adoption of new techniques. Table 11 classifies death from hæmorrhage into three groups with their incidence of avoidable factors. Table 12 gives an analysis of postpartum hæmorrhage

Table 11

MATERNAL DEATHS

HAEMORRHAGE, 1952 – 60.

	No.	Deaths with Avoidable Factors	
ACCIDENTAL HAEMORRHAGE	162	81	50%
PLACENTA PRAEVIA	82	47	57%
POSTPARTUM HAEMORRHAGE	244	148	61%
TOTAL	488	276	57%

Table 12

MATERNAL DEATHS

POSTPARTUM HAEMORRHAGE, 1952 – 60.

	Retained Placenta			Other Causes			Total		
	No.	Avoidable Factors		No.	Avoidable Factors		No.	Avoidable Factors	
1952–53	53	47	89%	60	33	55%	113	80	
1955–57	24	14	58%	46	23	50%	70	37	
1958=60	15	8	53%	46	23	50%	61	31	
TOTALS	92	69	75%	152	79	52%	244	148	61%

deaths. The first Report provided an impetus to create Flying Squads necessary to service all England and Wales, and to ensure that they were used. Their success is measured in part by the fall of 72% in the number of postpartum hæmorrhage deaths associated with retained placenta, and of 46% in hæmorrhage deaths from all postpartum causes (Table 12). The avoidable factor incidence in the two groups fell from 89% to 53%, and from 70% to 51%.

Another explanation for the fall in the number of deaths from postpartum hæmorrhage with retained placenta from 53 in the first triennium to 15 in the last is an improved standard of care in third stage management. There are two reasons for this. The first is a wider judicious use of oxytocic preparations, and the second is a change from expectant conservatism to intelligent active intervention. Both can now be regarded as the "best current practice" but both have dangers and used incorrectly could provide avoidable factors. For this reason they will be considered in some detail.

(a) Oxytocic Preparations

Whatever preparation is used, and by whatever route it is administered, the best effect is obtained with maximum safety when it is given in the second stage *once the anterior shoulder has been delivered*. It should not be given with crowning of the head or with delivery of the first infant in a multiple pregnancy. Both mistakes are commonly made and can occasionally cause the death of infant or mother. The danger with a single fœtus, particularly if large as with a diabetic,
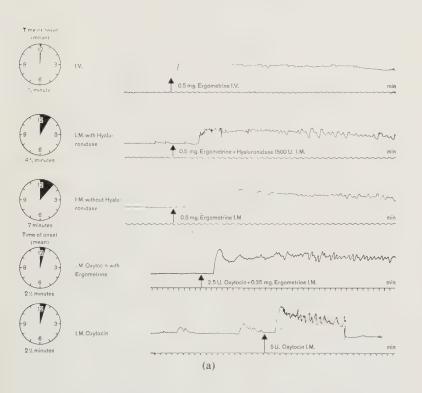
is that shoulder dystocia not only becomes more difficult to handle with the uterus tightly contracted round the fœtus but there is a possibility of uterine rupture. In multiple pregnancy there is danger to the second infant of intra-uterine asphyxia and the risk of rupture is increased by malpresentations, particularly in multigravidæ.
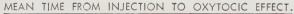
Tocographic studies showed that the synthetic hormone oxytocin acts more quickly than ergometrine after intramuscular injection, but its action is less sustained and delayed hæmorrhage is more likely to occur (Embrey, 1964). This suggested that oxytocin and ergometrine could be used together with advantage. The introduction of syntometrine, a stable preparation of ergometrine maleate 0·5 mg. and oxytocin 5 units in 1 ml., made an assessment of this possible.

Embrey (1961) found that the latent period between intramuscular administration of ergometrine and the uterine response is approximately 7 minutes. The same dose intravenously takes approximately 45 seconds. Intramuscular ergometrine combined with hyaluronidase (Kimbell, 1958) reduces the latent period to 4 minutes 47 seconds. Oxytocin intramuscularly is effective in $2\frac{1}{2}$ minutes, as is syntometrine. Both preparations are therefore nearly three times as rapid in their action as intramuscular ergometrine alone, and nearly twice as rapid as ergometrine with hyaluronidase (Fig. 3a and b).

The clinical advantage of using oxytocic preparations has been described by many authors. Daley (1951) published the results of giving 0·5 mg. ergometrine to 490 women in labour when the head was crowned. Postpartum hæmorrhage was reduced from 15·7% to 9·2% without increasing the need for manual removal of the placenta or the incidence of contraction rings. Kimbell (1958) analysed 4,651 labours conducted by midwives who gave intramuscular ergometrine with hyaluronidase and the incidence of postpartum hæmorrhage was 1·9%. Manual removal of the placenta was performed in 1%. Rowe (1962) compared the effect of intravenous ergometrine and intramuscular ergometrine during and after the end of the second stage, and of intramuscular ergometrine after the placenta was delivered. It was considered to be retained if not delivered within 20 minutes. Intravenous ergometrine given during the birth of the infant was the most effective technique and was associated with an incidence of 1·2% of postpartum hæmorrhage and 2·3% of manual removal of placenta. This latter incidence was more than double that reported by Kimbell, but postpartum hæmorrhage was less.
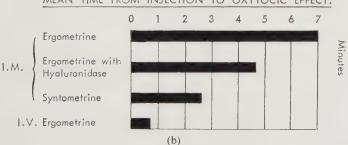
FIG. 3a & b. Oxytocic Preparations—Speed of Action. (These figures were kindly supplied by Mr. M. P. Embrey and published by courtesy of TRIANGLE, the Sandoz Journal of Medical Science.)

McGrath and Browne (1962) investigated syntometrine in domiciliary practice on the District of the Rotunda Hospital in a controlled series of 160 patients. One ml. of syntometrine was given intramuscularly to 80 during the end of the second stage by the midwife and to the remaining 80 ergometrine was given after delivery of the placenta. The average duration of the third stage was reduced from 20 minutes in the control group to 10 with syntometrine. Four patients had postpartum hæmorrhage in the syntometrine series with an average loss of 23 oz. (653 ml.), compared with 5 and an average loss of 29 oz. (824 ml.) in the control group. While there appears to be little difference as far as postpartum hæmorrhage is concerned the midwives were delighted because of the general decrease in third stage bleeding, which is particularly important in a community in which iron deficiency anæmia is common.

In a four-year study of 6,445 consecutive deliveries de Villiers and du Toit (1963) investigated the action of intramuscular oxytocic injections. They concluded that in both normal and abnormal deliveries postpartum hæmorrhage was reduced from $11 \cdot 98\%$ to 2% by the administration of an oxytocic drug irrespective of whether ergometrine, methergin, or syntometrine was used. The emphasis given by these and other authors to crowning of the head in preference to delivery of the anterior shoulder as the optimum time for injecting ergometrine or its equivalent raises an important point. The only logical explanation of reduced bleeding when the injection coincides with crowning of the head is that there is then normally a longer interval until delivery than there is once the anterior shoulder is delivered. If the infant is delivered slowly as recommended by Embrey the same optimum result will follow injection with delivery of the shoulder, and there will be added safety in not having a sustained powerful contraction complicating shoulder dystocia should this complication arise.

The administration of ergometrine or methylergometrine intravenously was advocated by Davis (1940) and good results were confirmed by Lister (1950) and Martin and Dumoulin (1953). Its great advantage is rapidity of action (Fig. 3) so it is of particular value in the anæsthetized patient and after prolonged or complicated labour. The effect on postpartum hæmorrhage, retained placenta, and manual removal is not realistic without reference to management of the third stage, and because the combination of oxytocic preparations with active intervention is increasing, reference will be made to it. We consider this to be an advance in the practice of obstetrics.

(b) Active Intervention in Third Stage

Senior obstetricians of today were taught as medical students that cord traction was an obstetrical mortal sin. Now many of them teach that with certain clearly defined precautions it is an essential part of correct third stage management. The wheel has turned full circle.

History. In an excellent review Hibbard (1964) referred to the teaching of Aristotle that cord traction should be used "to bring away the after-burden, for it can prove dangerous if it be not speedily done." In the nineteenth century, because it was believed that the cervix closed after the baby was born and imprisoned the placenta, cord traction and early manual removal were practised. There was a high mortality from hæmorrhage, shock and sepsis and other techniques were explored. They included abdominal binders with pads to maintain intra-abdominal pressure and assist the uterus in expelling the placenta. Remedies for hæmorrhage varied from injecting iced water into the uterus to douching with hot water as suggested by Trousseau (1853). That same year Credé published his technique, which heralded the end of immediate termination of the third stage by cord traction or manual removal. A method similar to Credé's was used at the Rotunda for many years before this paper was published (McClintock and Hardy, 1848). Kirkpatrick (1915) records that Smellie's assistant and successor, John Harvie, described the same technique in 1767.

Credé's method, whether original or not, was a great advance. Introduced to avoid unnecessary manual removal it encouraged a conservative attitude with termination of the third stage by con- trolled expression of the placenta from a contracting uterus only when necessary, but its abuse led to ill-considered fiddling with the relaxed uterus. Designed to prevent postpartum hæmorrhage it became a common way of causing it and when unsuccessful attempts at placental expression were repeated the danger of shock was added.

When Flew (1947) advocated the administration of ergometrine after delivery of the head it was thought by many to be obstetrical heresy, but the reduction of hæmorrhage was a major contribution to practice. The combination of an oxytocic preparation and judicious active intervention is a logical development and gives promise of being a further advance.

Active Intervention. Brandt (1933) taught that once the cord was divided it should be held firmly in one hand while the other, placed above the pubis, gently elevated the uterus towards the umbilicus

and in this way assisted placental separation and expulsion. Andrews (1940) had similar ideas, hence the term Brandt-Andrews manœuvre. Spencer (1962) described a modification taught to students at University College Hospital in which intravenous ergometrine 0·5 mg. is given with delivery of the anterior shoulder prior to controlled cord traction. This is increased as necessary but only when the fundus is contracted and supported. In 1,000 consecutive deliveries conducted in this way the third stage was uneventful in 97%. Postpartum hæmorrhage occurred 12 times (1·2%) and manual removal 15 times (1·5%). Acute inversion of the uterus did not occur, but the cord broke 26 times and was followed by manual removal on 7 occasions.

Embrey *et al.* (1963) tested the effect of syntometrine on 1,180 normal deliveries supervised by midwives. Active management of the third stage was practised by fundal expression of the placenta when the uterus contracted strongly. Five hundred and ninety patients were given intramuscular syntometrine and 590 ergometrine 0·5 mg. when the anterior shoulder was delivered. The results supported the findings of Chukudebelu *et al.* (1963) and of Kemp (1963) by demonstrating the advantage of syntometrine over ergometrine. The incidence of postpartum hæmorrhage was 2·9% with syntometrine and 6·6% with ergometrine, whereas the incidence of manual removal was comparable, 1·5% and 1·4% (Table 13). There was a greater incidence of hæmorrhage with multigravidæ,

Table 13

COMPARISON OF SYNTOMETRINE & ERGOMETRINE.

(Embrey, 1964)

A. Total series	Number	Postpartum haemorrhage	Manual removal of placenta
SYNTOMETRINE	590	2.9%	1.5%
ERGOMETRINE	590	6.6%	1.4%
B. Primigravidae			
SYNTOMETRINE	208	2.4%	2.4%
ERGOMETRINE	187	4.8%	2.7%
C. Multigravidae			
SYNTOMETRINE	382	3.1%	1.0%
ERGOMETRINE	403	7.4%	0.8%

3·1% after syntometrine and 7·4% after ergometrine. Corresponding figures in primigravidæ were 2·4% and 4·8%. The incidence of postpartum hæmorrhage was halved when syntometrine was used with active intervention. No patient to whom syntometrine was given lost more than 30 oz. (852 ml.) and blood transfusion was necessary only once. With ergometrine the loss exceeded 852 ml. 12 times and 20 patients required transfusion. The probable explanation of increased bleeding with ergometrine lies in the time lag of 7 minutes between its injection and action, compared with $2\frac{1}{2}$ minutes for syntometrine. *This merely emphasizes the importance of correlating the speed of delivery with the rapidity of action of the drug used according to its route of administration.* Risks are minimized by delivering the baby slowly and when timing is correct the placenta is expelled as the buttocks are born. With correct technique there is no greater danger of retained placenta with syntometrine than with ergometrine. If the placenta is not expelled immediately following delivery Embrey (1964) advocates active intervention using the Brandt-Andrews method.

Hibbard (1964) emphasized that the risk of hæmorrhage is related directly to the time interval between delivery of infant and placenta, rising steeply to over 30% if the third stage is prolonged for more than 30 minutes. Like Embrey he favours the use of intramuscular syntometrine and active intervention in the third stage. The three techniques available are demonstrated in Fig. 4*a*, *b*, *c*. To advise that the correct management of the third stage demands active intervention is a revolution of thought and practice, but as old prejudices are forgotten and the new method is used more extensively it is reasonable to expect a further fall in the mortality from hæmorrhage.

Acute Inversion of the Uterus. Most medical techniques have dangers, particularly when used incorrectly. When the uterus is well contracted strong traction may break the cord, but if the uterus is relaxed, excessive traction may result in acute inversion. When this occurs the risk is directly proportional to the time it is allowed to persist. Immediate replacement is the correct treatment. The time available before the oxytocic drug contracts the uterus depends on its route of administration. For this reason inversion is considerably less common after intravenous administration, but should it occur seconds are important in replacing it. The Newcastle Emergency Service has been summoned 20 times to uterine inversion (Stabler, 1964). Three patients were dead when the team arrived, but the remainder were all saved by immediate manual replacement without waiting to combat shock or hæmorrhage.
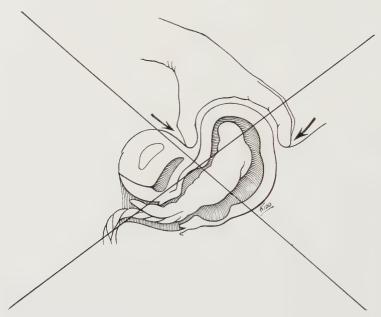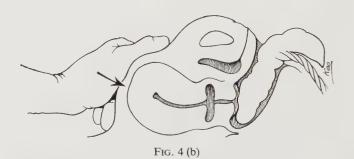
FIG 4 (a)

FIG. 4 (b)

FIG. 4 (c)

FIG. 4a, b & c. Third Stage Management.
    (a) Crede expression   }
    (b) Fundal pressure   } not advised
    (c) Brandt-Andrews technique—advised.
            (Hibbard, B. M. (1964). *Brit. med. J.*, 1, 1485).

Third Stage Management. The following procedure, designed for maximum safety in the conduct of the third stage of labour, is suggested as a guide to practice in home or hospital.

1. The bladder should be emptied prior to the end of the second stage of labour. A full bladder can delay placental expulsion.

2. With a normal delivery conducted by a midwife, general practitioner or student, syntometrine 1 ampoule, or if this is not available 0·5 mg. of ergometrine with hyaluronidase, should be given intramuscularly once the anterior shoulder is visible beneath the symphysis.

3. Delivery of the infant is allowed to take place slowly once its airways have been cleared, taking at least 2 minutes.

4. If the placenta is not expelled immediately following the birth of the child active intervention is practised by the Brandt-Andrews technique with the precautions already described.

5. When a doctor is in attendance at a delivery complicated by forceps, breech or multiple pregnancy, and particularly when a patient is tired after a long labour with associated inertia, or if delivery is performed under general anæsthesia, or there is a history of hæmorrhage, intravenous ergometrine 0·5 mg. given after delivery of the anterior shoulder is the method of choice. With a breech delivery the ergometrine is given when the head is in the vagina, and in multiple pregnancy only with delivery of the last infant.

6. When intravenous ergometrine is advisable, but the doctor is working without adequate assistance, the preliminary insertion of a Gordh or Mitchell needle into a vein on the back of the hand makes it possible for an untrained assistant to give the injection when instructed. Bender (1964) referred to the use of this technique in domiciliary practice.

N.B. The emphasis throughout is on slow delivery of the baby and rapid delivery of the placenta.
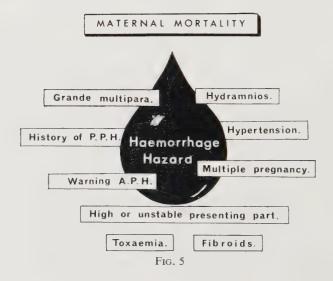
A mismanaged third stage in what should be a perfectly normal delivery can bring disaster, but postpartum hæmorrhage can occur for other reasons. The Enquiry has shown that a recurring avoidable factor has been booking patients for delivery in the wrong place. Many at greater risk than normal from hæmorrhage were booked for home confinement, delivery in general practitioner units, or in private nursing homes.

A grand multipara with a history of postpartum hæmorrhage was booked for delivery at home. Her care in labour was entrusted to a midwife. Hæmorrhage occurred immediately after delivery and medical aid was summoned, but the doctor arrived $1\frac{1}{2}$ hours later. There was a Flying Squad in the area, but it was not called and the patient by now gravely ill, was sent to hospital where she arrived moribund.

A corollary to this was a death recorded in the 1963 Report.

A multipara with a history of postpartum hæmorrhage was booked for delivery at home. Third stage bleeding occurred and a Flying Squad was summoned, in spite of which she died. Review of the case suggested that treatment by the emergency team had not been in accordance with the "best current practice".

High-risk Patient. Patients with an increased risk of hæmorrhage (Fig. 5) should be booked for delivery in hospital under consultant supervision. Anæmia must be prevented, or treated when it occurs. This necessitates estimating the hæmoglobin level at the first visit and early in the last trimester as a minimum and more frequently

MATERNAL MORTALITY

Grande multipara.   Hydramnios.

History of P.P.H.   Haemorrhage Hazard   Hypertension.

Multiple pregnancy.

Warning A.P.H.

High or unstable presenting part.

Toxaemia.   Fibroids.

Fig. 5

when it or the response to iron is unsatisfactory. Intramuscular or intravenous iron therapy or blood transfusion in the later weeks with their disadvantages and dangers (Chapter 3) can usually be avoided by efficient antenatal care. The anæmic woman who goes into labour starts at an unjustifiable disadvantage, yet the Enquiry revealed that even in 1963 hæmoglobin estimations were recorded in only 48 % of those who died from hæmorrhage, and in 36·9 % of all maternal deaths.

Other important avoidable factors are failure to appreciate the severity of hæmorrhage, failure to ask in time for consultant help, including Flying Squads, and delay in starting transfusions. Twenty-nine maternal deaths (1952–60) followed transfer of patients to hospital with the placenta undelivered. It was to handle just this type of emergency that the Flying Squad was first instituted and the greater the distance to be covered the more dangerous it is not to treat the patient at home. The role of the modern obstetric flying squad has been reviewed by Massouras and Seedat (1964).

Placenta Prævia

Placenta prævia deaths have shown little improvement throughout the Enquiry. Good results reported from Belfast by Macafee and his colleagues (1945,1962), from Oxford by Stallworthy (1950, 1951a, 1951b) and from London by Percival and Murray (1955, 1959, 1960a, 1960b) to mention but three centres, suggest that the treatment of this serious complication must often depart from "best current practice". In a well-organized obstetric service there should be few deaths from hæmorrhage of any type. Stallworthy (1950) claimed that no woman with placenta prævia should die and the fœtal loss should not exceed 10 %. At that time the mortality from this condition was 3 % and fœtal loss 36 % in a collected group of teaching hospitals. In the years 1940–63 542 women with placenta prævia were delivered at Oxford without a death from this complication of pregnancy. There was one associated death in a young woman with extensive nasopharyngeal carcinoma, who was safely delivered by section. She died later in a surgical ward from cancer involving the base of the skull, and autopsy confirmed the cause of death. The following practical details in diagnosis and treatment have been emphasized by Macafee, Stallworthy and others.

Diagnosis

A high unstable presenting part in the later weeks of pregnancy is important *before hæmorrhage occurs*. The corollary for safety of both mother and baby is that vaginal examination *must not be*

2*

performed at home or in a general practitioner unit but always in a well-equipped theatre ready to proceed to Cæsarean section. Failure to observe this rule is still a recurring avoidable factor. When emphasizing the danger of vaginal examination it is easy to forget that rough abdominal palpation can provoke bleeding particularly when the placenta is anterior. Walker *et al.* (1963) quoted the following cases:

The doctor did not send the patient to hospital after a small antepartum hæmorrhage. He twice examined her vaginally at home, the second examination being followed by catastrophic hæmorrhage.

The worst example was a gravida 8 over 40 years old whose previous confinements had been anything but straightforward, who had previously had Cæsarean section performed and whose confinement was planned to take place in a small maternity home. She developed a sharp antepartum hæmorrhage for which the doctor performed "an emergency Cæsarean section". Her condition at the time was noted to be bad and no blood was available. She died.

The Oxford approach to placenta prævia excludes routine vaginal examination in antepartum hæmorrhage. It is not performed if a transverse or oblique lie is associated with bleeding, but is reserved for patients with an unstable presenting part which can be made to fit into the pelvis at or near term, and those who are bleeding in the later weeks of pregnancy with a vertex presenting. If the presenting part engages and bleeding stops a vaginal examination is not made. In other words, it is confined to the selected groups specified in which a decision has to be taken whether to deliver vaginally or by section. For this reason many patients who almost certainly have a minor degree of placenta prævia (in whom the position of the placenta is not confirmed because vaginal examination is not made) are included in the group of antepartum hæmorrhage of unknown origin. This means that the diagnosed series has a higher proportion with a major degree of placenta prævia which makes the results the more encouraging.

Macafee (1962) stated that:

. . . in England and Wales from 1942 to 1949, 395 women died from placenta prævia, a complication which if properly treated should be associated with a maternal mortality of almost nil. From the Report on Confidential Enquiries into Maternal Deaths we find that from 1952–54 29 women died and in 55% of these deaths there were avoidable factors. Despite all that has been written and taught on the subject the years 1955–57 showed little or no improvement as 28 women died and in 43% there were avoidable factors.

He reviewed some basic facts of diagnosis and treatment and stressed the possible significance of malpresentations in late preg-

nancy even without bleeding. In a Belfast series of placenta prævia patients the vertex presented in 68%, breech in 12·6% and in 20% there was an oblique or transverse lie. The fœtus should be viable at the 36th week and if the presenting part is high, unstable, or there is a malpresentation, or bleeding makes intervention necessary, active treatment begins with examination in the theatre. If bleeding is severe and the presenting part is unstable, or there is a breech or transverse lie, immediate section should be performed *without vaginal examination* which may provoke further bleeding and will waste time. Whatever the findings, they should not affect the decision to operate, and *there is therefore no point in the examination*. Vaginal delivery was associated with a fœtal mortality of 42·3% when the fœtus presented by the breech or was lying transversely, whereas with Cæsarean section under similar circumstances it was 5·7%. When a vertex presents and enters the brim the forewaters should be ruptured even with a posterior placenta prævia, but the patient should not then be left unattended. A persistently disturbed fœtal heart indicates distress and even in the absence of bleeding the table should be tipped to lift the head from the pelvic brim, oxygen should be administered, and section performed. In such cases the cord is often attached low on the placenta and is compressed by the head. Prompt recognition and immediate section will save the infants' life.

Expectant Attitude

When the fœtus is not viable or the diagnosis is in doubt before the 36th week, the expectant attitude first advocated by Macafee (1945) and Johnson (1945) is indicated. This is all very well in an adequately staffed hospital but in some places, as for example in crowded institutions on the African continent, the conservative approach would be impracticable and often unjustifiable. Under such circumstances intervention at the time of bleeding, even though the infant is premature, may be necessary for the safety of the mother. It should follow the lines already described but the earlier the need to interfere the greater the chance of section being the safest procedure. If bleeding is severe a Flying Squad should accept responsibility for transfer of the patient to hospital and the longer the distance she has to travel the more necessary this precaution becomes.

Accessory Diagnostic Aids

With bleeding before the 36th week the desire to make a definite diagnosis without resorting to pelvic examination has led to the development of accessory techniques. If antepartum hæmorrhage

of placental origin is regarded as always being associated with increased fœtal risk, fewer patients would be sent home when placenta prævia is excluded. Methods involving radiation for placental localization then become academic, and in the opinion of many unjustified.

A transverse or oblique lie without bleeding before the stage of viability presents a different problem and in this group the various diagnostic techniques can prove helpful. Even so, many obstetricians prefer to rely on clinical judgement rather than to submit mother and fœtus to radiation. We agree with Macafee in this view. Nonetheless, techniques now to be described can localize the placental site with accuracy but as a preliminary to conservative management *speculum examination of the cervix is essential.*

Inspection of Cervix

It is dangerous *not* to make a speculum examination. Carcinoma is sometimes forgotten as a cause of antepartum bleeding and although it does not exclude a placenta prævia *it is a contra-indication to conservative inactivity.*

Some doctors assume that if vaginal examination is not permissible except in a theatre, this also applies to inspection of the cervix. Under many circumstances this is correct. A finger inserted in a patient's home or a doctor's surgery may provoke fatal hæmorrhage and even abdominal examination or gentle palpation through the fornices can start disastrous bleeding from a placenta prævia. The gentle insertion of a Sims speculum will not do this but will reveal a polyp or a carcinoma, whereas a bivalve speculum stretching the vault may provoke bleeding. If the conservative treatment of antepartum hæmorrhage leads to the discovery of a carcinoma weeks later a grave mistake has been made. If, however, there is a malpresentation, or a high head, the patient should be referred for consultant opinion without either vaginal examination or cervical inspection.

Radiological Techniques

Reid (1949) described the simplest method, effective only with a vertex presentation, requiring one film taken laterally with the patient semi-erect. Crawford *et al.* (1957, 1961), Earn *et al.* (1958), and Percival and Murray (1960a, 1960b) use placentography to help them decide whether to keep in hospital a patient with a small hæmorrhage before active intervention is justified.

Retrograde Aortic Placentography

Hartnett (1948) demonstrated the placenta by translumbar aortography, and the injection of contrast medium into the femoral artery was used by Sutton (1952). The diagnostic possibilities were apparent, but there were technical difficulties, serial films were necessary, and the radiation dose was not insignificant. Seldinger (1953) used arterial catheterization and the technique has been adopted by de Villiers and Brink (1957), Sutton (1962), and others. A single film technique was described by de Villiers and Brink (1957) and Brink (1960).

Technique. A retrograde aortogram is performed by catheterizing the femoral artery just below the inguinal ligament. A polythene catheter inserted for 22·5 cm. with a patient of average build has the tip just above the bifurcation of the aorta. This eliminates an unnecessary exposure to determine its position. 50 ml. of $3·8\%$ sodium citrate in 300 ml. saline is infused. The patient is centred on a 14 by 17 cassette and urografin (25 ml. of 76% solution at body temperature) is injected under pressure. Exactly 2 seconds later a film is taken while the patient holds her breath in expiration. If this is satisfactory the catheter is withdrawn and firm pressure is maintained for 10 minutes over the puncture. In 80% of patients examined by Basson and de Villiers (1963) only one film was required. If the placenta was not well defined and there was complete clearance of dye from the arterial system a further film was taken 1 second after another injection. When the placenta was poorly defined after 2 seconds but contrast medium was still visible in the pelvic vessels a delay of 3 seconds and occasionally 4 was allowed before taking a second film.

Eighty-seven placentograms were performed by de Villiers and his team for antepartum hæmorrhage. No placenta prævia subsequently demonstrated at section or on vaginal examination was missed radiologically. Three errors related only to the degree of placenta prævia estimated, a type 1 posterior proved to be type III, and two type II were central. Twenty-nine of these patients were less than 32 weeks pregnant and only 2 were kept in hospital because of a radiological diagnosis of placenta prævia. The remaining 27 were discharged and admitted for induction at 38 weeks.

Complications. Three patients developed a minor hæmatoma. Increased uterine activity lasting a few seconds sometimes followed the injection. There were no arterial complications, but in older patients atheromatous plaques have been dislodged and amputation has been necessary following aortic catheterization, a reminder that

the method can be dangerous. Medico-legal implications are considered in Chapter 9. Brink (1960) reported 200 placento-graphies with no serious complications.

Radioactive Isotopes

Techniques involving the use of these substances have been employed for placental localization by Weinberg *et al.* (1963) and others. Isotopes, tagged to red cells, given intravenously emit gamma particles which are identified by surveying the abdomen with an appropriate detector. Areas of maximum intensity indicate pools of blood. Radioactive iodine 131 and 132 have the disadvantage of crossing the placental barrier and may be stored in the maternal or fœtal thyroid. Chromium 51 is free from this disadvantage and was used by Gahres *et al.* (1962) to estimate the normal antepartum red cell volume. Paul *et al.* (1963) used the same technique to localize the placenta and examined 106 patients, of whom 26 had a small antepartum hæmorrhage. Central placenta prævia was confirmed in 33 at Cæsarean section and in 71 of 73 patients with lesser degrees of placenta prævia who were delivered vaginally the exact site was confirmed by intra-uterine exploration before separation of the placenta. The only error was associated with a vascular fibromyoma in the lower segment. This caused a mal-presentation and was thought to be a placenta prævia. After delivery the myoma and placenta revealed equivalent radioactivity, although fibroids do not usually interfere with placental localization.

Roux of Cape Town, in a personal communication, states that he has used chromium 51 in 100 mc. doses and the fœtal cord blood 24 hours after the maternal injection showed no sign of activity. In over 100 patients the method effectively localized the placenta and gave a lower radiation dose than X-ray. It was less accurate before the 32nd week, when correct diagnosis would be of most value. Those who prefer not to use radiation in any form for placental diagnosis, and those for whom facilities do not exist, may take comfort from the fact that good antenatal and intrapartum care is fundamental to success as stressed by Macafee.

Thermography

Lloyd Williams and Cade (1964) demonstrated that the body emits and reflects infra-red radiation with a rate of flow in dynamic equilibrium with the environment. Young (1964) applied these principles to localize the placenta. He studied 47 patients and was

able to demonstrate accuracy of prediction in 13 who came to section. The patient was maintained at a temperature of between 20°–23°C. in a small room. Surface application of cold towels produced vaso-constriction as shown by Lloyd Williams *et al.* (1960–61) and emphasized thermal contrast, but no pregnant woman objected to the discomfort of this. Thermographs recorded by a Pyroscan can be difficult to interpret without experience but the technique is interesting and obviates the disadvantages of ionizing substances.

Conclusion

Efficient treatment for placenta prævia, as for all other obstetric emergencies, begins at the first antenatal visit. Careful attention to general health, particularly in treating anæmia, and the correct selection of place for delivery can prove life-saving when hæmorrhage occurs. When bleeding is catastrophic the difference between life and death can be measured in minutes, and survival may depend on where the patient is at the time. Hæmorrhage at operation can be sudden and terrifying and the patient requiring Cæsarean section for placenta prævia is not suitable for the unsupervized care of a junior specialist in training. Transfusion should begin before the patient is anæsthetized, but if this is not done a saline infusion makes it possible to substitute blood speedily should this become necessary. A pump increases the safety margin.

Among the 16 placenta prævia deaths with avoidable factors the fault in management lay usually in failure to take action until too late. . . . The time to consider blood transfusion is before and not after the appearance of signs of collapse (Walker *et al.*, 1957).

The remaining two major causes of maternal death are abortion and pulmonary embolism, which together accounted for 846 (31%) of 2,697 deaths. There has been little reduction since 1952 (Table 9), but their relative importance has increased. In 1961–1963 abortion was the major cause of maternal death with embolism second and toxæmia third.

Abortion

A slight fall in the number of deaths has occurred (Table 9) in spite of a rising birth rate, but the position is unsatisfactory. There are important social and economic as well as medical factors to consider.

Criminal abortions caused at least 281 (65%) of 429 abortion deaths (1952–60) and approximately 60% of the women were

Table 14

CRITICAL: CRIMINAL ABORTION, 1952-57.

Cause of Death	
SEPSIS	105
AIR EMBOLISM	43
HAEMORRHAGE & SHOCK	22
ANURIA	18
NOT STATED	11
TOTAL	199

married, many with families. Table 14 summarizes the mode of death. Infection, now a minor cause of maternal deaths, was responsible for 53% following criminal abortion.

Fortunately those who die represent a relatively small percentage of women whose pregnancy is terminated but the implications of this waste of life and associated suffering concern the community as well as the doctors. Physical and mental health is impaired in many who survive. The expanding activities of the Family Planning Association provide one constructive approach to this problem. Sepsis, hæmorrhage, shock and renal failure also cause deaths associated with spontaneous or therapeutic abortion. For this reason principles established as essential to the safe care of these patients are emphasized, and reference is made to recent promising developments.

The soft pregnant uterus is easily perforated and the danger is reduced by making certain of its exact position and by promoting contractions before exploring the cavity. Dilators easily perforate the anterior wall of a retroverted gravid uterus thought to be anteverted; and similarly a uterus wrongly thought to be retroverted can be perforated through its posterior wall. Ovarian or uterine tumours increase the danger. If intravenous ergometrine (0·5 mg.) is given before the bladder is emptied and the uterine position is confirmed the contracted organ reduces the risk of hæmorrhage and perforation. Gentleness increases safety.

When exploration is necessary 7–14 days after abortion two further dangers are added, infection and postoperative intra-uterine adhesions. Infection, even without pyrexia, is often present and *if the uterus is tender the risk is increased*. It causes further softening of the myometrium which can be ruptured by opening and rotating

ovum forceps within the cavity. Digital exploration is safer when dilatation makes this possible. As infection may spread it is wise to take uterine cultures for aerobic and anaerobic organisms and sensitivity. Delayed shock and anuria due to infection make this precaution even more necessary. Curettage 10–14 days after delivery or abortion carries the risk of removing too much decidua and even myometrium with the formation of synechiæ. A practical point is that a sharp curette should not be used at this critical time (Chapter 7). If myometrium is in the curettings the risk is increased and the patient should be kept under review.

Therapeutic Abortion

Views on the indications for this procedure vary from the two extremes that it is never justifiable to an attitude made more liberal by the inclusion of mental stress, and the possibility of fœtal abnormality. Legal implications are discussed in Chapter 9. The gynæcologist must accept responsibility for whatever decision he makes but if he feels that interference is indicated he still has a problem to solve. It concerns the best method to use.

In the early weeks of gestation the quickest and safest technique is by the one stage procedure of dilatation and evacuation with the precautions already described. The question of what stage of gestation marks the maximum for safe vaginal evacuation varies with the surgeon, but guiding principles can help the decision. Uterine size is more important than the period of amenorrhœa, which can be misleading; the smaller and more contracted the uterus is, the less the danger of hæmorrhage and perforation. Intravenous syntometrine 1 amp., or ergometrine (0·5 mg.), given at least 1 minute before passing the first dilator is a wise preliminary. The slow passage of each dilator reduces the danger of cervical trauma, and leaving it in the canal for a few seconds before using the larger size promotes uterine contraction and reduces bleeding. If hæmorrhage is troublesome a blunt flushing curette using saline at a temperature of 118°F. (84°C.) has a similar effect and removes debris.

Hysterotomy

With a uterus larger than the size of a 12 weeks gestation and palpable abdominally many surgeons perform either abdominal or vaginal hysterotomy. If tubal ligation is indicated the former is preferred but both techniques carry the delayed risk of implantation

endometriosis. Legalized abortion provides Swedish clinics with a large experience of these patients and several thousand terminations are performed annually. Vaginal hysterotomy was favoured until vault endometriosis became a problem (Brosset, 1954) and the younger the patient the greater the risk. New techniques were explored with the adoption of the intra-uterine injection of 20% saline or 50% glucose (Brosset, 1958). *Clostridium welchii* and anaerobic streptococci flourish in a glucose rich environment (Kemp and Vollum, 1946) so sodium chloride is safer, a view shared by Pinkerton (1964).

Saline Injection

Both abdominal and vaginal techniques have in common the removal of as much liquor as possible through an 18 gauge needle of approximately 15 cm. length and its replacement with a corresponding volume of up to 200 ml. of 20% sodium chloride solution. Wiqvist (1964) advocates this as a safe and rapid method of emptying a uterus. Aseptically he inserts the needle through the midline directly over the uterus and through its fundus. Gentle curettage is performed 12 hours after the fœtus is expelled providing the uterus is not larger than the size of a 20 weeks gestation. Fuchs (1964) favours the vaginal route between the 13th and 18th week of pregnancy and inserts the needle through the anterior fornix. The average time for expulsion of the fœtus is 36 hours but it is much quicker with a missed abortion. No serious infection has been reported with 20% sodium chloride, an important observation as 53% of deaths from procured abortion (58 in 108) and 47% from other abortions (21 in 45) were due to sepsis in the total of 153 analysed in the 1952–54 Report (Walker *et al.*, 1957).

Injection techniques are simple and effective—when they work. It can be surprisingly difficult however to locate the amniotic cavity by either route, particularly early in pregnancy. The more manipulation required the greater the danger of damaging the uterus or adjacent structures, and it is important to define its exact position before the needle is inserted. The larger the uterus the easier the injection. If the amniotic sac cannot be located by the exploring needle, particularly by the vaginal approach, a useful modification of the technique is to insert a Foley type catheter through the cervix, inflate the balloon end with 5–10 ml. of saline and slowly inject 150–200 ml. of 20% sterile saline which enters the extra-amniotic space. The catheter is left in position for 12 hours if it is not expelled before this.

Gellen *et al.* (1965) have demonstrated that the number of erythro-cytes containing fœtal hæmoglobin in the maternal circulation is increased after evacuation of the uterus in even the first 8–12 weeks of pregnancy. This suggests the possibility of an immunising role in the presence of fœtal-maternal rhesus incompatibility. If this occurs the termination of even a first pregnancy could sensitise the mother and prejudice her future obstetric performance.

Three deaths in London and 2 in the provinces following saline injection have occurred since this section was written but have not yet been published. Exact details are not available but coma preceded death and the brains so far examined revealed focal hæmorrhages and degeneration of the amygdaloid nuclei. It is difficult to under-stand the mechanism of this complication but until more facts are known the possible danger should be realised. Brosset (1966, personal communication) has used glucose extensively without a maternal death.

Vacuum Suction

Chernyak (1963) used this on 600 patients between the 6th and 12th weeks of pregnancy and claims that a negative pressure of $0\cdot5$–$0\cdot6$ atmosphere breaks up and extracts the conceptus painlessly through a hollow suction tube in 1–$2\frac{1}{2}$ minutes. Contra-indications are—sepsis, an interval of less than 6 months since the last abortion, pregnancy of more than 12 weeks duration, and acute infectious disease. Advantages are minimal bleeding, less danger of trauma-tising the uterus, and rapid evacuation.

Septic Shock

Toxic shock due to infection is characterized by hypotension and intense erythema with warm extremities and a mortality of 60% in 41 cases reviewed by Stevens *et al.* (1953). They described the syndrome as "red shock", in contrast to the peripheral failure and cold limbs seen in *Clostridium welchii* septicæmia or in adrenal hæmorrhage or infection. Gram negative coliform organisms are usually responsible as in 3 patients described by Dumoulin and Steed (1956), but staphylococci and streptococci have been isolated and may be introduced by surgical induction and transfusing infected blood. Pittman (1953) described 16 cases with 9 deaths and Hall and Gold (1955) reviewed 35 patients with shock in a total of 100 with bacteræmia. Lane (1955) described fatal post-partum hæmorrhage and collapse due to coliform organisms and hæmolytic streptococcal septicæmia after hysterectomy for accidental hæmorrhage.

Though relatively rare, the condition is important for two reasons:—
it is easily overlooked and is amenable to treatment with antibiotics,
intravenous hydrocortizone and blood transfusion. Overloading the
circulation is particularly dangerous because of the toxic myocar-
dium. Douglas *et al.* (1964) stated that septic shock due to abortion
was more common in older debilitated or chronically ill patients.
They devised a diagnostic test for Gram negative bacterial septic-
æmia which consists of injecting intravenously into a rabbit a sample
of patient's blood and then injecting 50–100 micrograms of adrenalin
in 0·2 ml. of 0·9% saline into its skin. The test is positive when
hæmorrhagic necrosis occurs at the site of injection. Clostridium
infection gave a negative test but 8 of 10 were positive with coliform
shock. Govan *et al.* (1962) demonstrated that multiple thrombi
blocking renal vessels, and not vascular spasm, were responsible for
cortical necrosis. Others have expressed the view that intravascular
clotting is the basis of this syndrome, in which case heparin therapy
would be rational as suggested by Sharp (personal communication).

The clinical manifestations of postabortal infection since the use
of antibiotic therapy can be insidious, particularly the hepatorenal
syndromes with jaundice appearing as a primary symptom. Following
abortion this should suggest the possibility of genital tract infection.

Renal Failure

Though important it is not common after abortion. Simpson
(1949) established it as the cause of death in only 2 of 100 autopsies,
and it was responsible for 6% of 108 deaths following procured
abortion (Walker *et al*, 1957) and for 12% in a further series of 91
(Walker *et al.*, 1960). The rising incidence may be apparent rather
than real. On the other hand, the number of abortion deaths is
falling, probably due to a decrease in air embolism, hæmorrhage
and sepsis and if this surmise is correct it will be reasonable to expect
that there may be an increase in the importance of renal failure.
The limited evidence supplied by Walker *et al.* (1957) would support
this view for although cortical necrosis caused death in 6% of fatal
criminal abortions it accounted for 8 of 45 deaths (18%) in spon-
taneous or therapeutic abortions in which no patient died from
air embolism.

The association of abortion with sepsis, shock and renal failure
is common at the Baragwanath Hospital, Johannesburg, where
approximately 2,000 Bantu patients are admitted annually with
abortions. Many, criminally induced, present the syndrome of

septic shock with renal failure. Anuria following abortion, uterine rupture, pre-eclampsia, eclampsia and concealed accidental hæmorrhage account for approximately 75% of all patients requiring dialysis. This was used in 1963 on 21 patients when the blood urea rose to 350 mg./100 ml. and the blood potassium to 5·5 m. equiv./litre or higher.

Cortical necrosis was found in only 2 of 180 autopsies performed on women registered as maternal deaths at Baragwanath. Lavery and Dugas (personal communication) believed that most obstetrical and gynæcological patients who develop anuria have a lower nephron lesion and that this is particularly common in abortion with septic shock. Most of these patients are shocked on admission with a clostridium or *E. coliform* septicæmia but others appear well, are curetted, discharged within 24 hours, and are readmitted several days later with anuria. Experience has shown that *uterine tenderness is more important than pyrexia* as a contra-indication to curettage for retained products. Since peritoneal dialysis has largely replaced hæmodialysis for these patients at Baragwanath the mortality has fallen from 75% to 25%. This important advance merits a brief summary of current views on uræmia and dialysis.

Uræmia

It is not certain exactly how anuria occurs and how diuresis takes place in those patients who recover. Oliver and his associates (1951) made a detailed study with microdissection of the kidney in acute renal failure due to trauma and toxæmia. They described two distinct tubular lesions. When failure was due to a nephrotoxin large segments of proximal tubules showed uniform cellular necrosis extending down to, but not including, the basement membrane. When ischæmia was associated with failure tubular continuity was disrupted, including dissolution of the basement membrane with secondary ingrowth of connective tissue elements, but many nephrons remained intact. Study by electron microscopy of renal biopsy sections in acute failure confirmed these changes and showed alteration in the mitochondria of tubular cells when anuria was associated with ischæmia, as described by Dalgaard and Pedersen (1959). Earlier suggestions that acute renal failure could be due to glomerular lesions do not appear tenable in the light of this evidence.

Bull and his colleagues (1950) attributed anuria to an inadequate renal blood flow which they found to be 5% or less of normal.

As the oxygen uptake was correspondingly reduced they concluded that glomerular filtration must be negligible. Brun (1955) using Krypton 85 demonstrated that renal circulation was reduced to half the normal value during the anuric phase of acute renal failure, but there appears to be doubt whether this precludes any appreciable persistence of glomerular filtration. The observation that renal blood flow and oxygen consumption are comparable during the anuric and early diuretic phases could indicate that continued filtration takes place.

Changes in body water compartments and their relation to water and electrolyte excretion were studied by Remenchik *et al*. (1958). A surplus of water results from the rapid catabolism of fat and protein during oliguria. Bluemle *et al*. (1956) estimated this at 303 plus or minus 30 ml. per 24 hours, and preformed water at 124 plus or minus 75 ml. They assessed the proper fluid intake from the daily weight loss which varies from 0·2 to 0·5 kg. in the average anuric obstetric patient. Attempts to prevent or minimize this increase the tendency to overhydrate, and in their opinion an average daily fluid intake of 400 ml., combined with renal and gastro-intestinal replacement, is sufficient to maintain fluid balance and prevent hyponatremia.

The elevation of serum potassium, characteristic of prolonged renal failure, is the result of potassium release from depleted glycogen stores, the destruction of red blood cells, the metabolism of protein and fat, and the extra cellular shift of potassium as a consequence of acidosis. Serum potassium levels rise at an average of 0·7 m. equiv./litre per day, frequently reaching 9 m. equiv. after 6 days of anuria. The liberation of large quantities of potassium from devitalized tissue, especially muscle, was emphasized by Meroney and Herndon (1954) who stated "excessive debridement may cost the patient previous tissue, but inadequate debridement may cost his life". A disproportionate rise in serum phosphate and serum creatinine as compared to non-protein nitrogen or urea nitrogen levels has been proposed as a possible diagnostic aid in the detection of devitalized tissue by Meroney (1955) and Doolan *et al*. (1959). These observations may help when anuria is associated with septic abortion or severe accidental hæmorrhage with myometrial destruction, and when response to treatment is poor it could be an argument in favour of hysterectomy.

Bluemle and his team have shown that in the presence of tissue necrosis or infection the rate of protein catabolism is minimally affected by even wide variations in caloric intake. The use of approxi-

mately 100 g. of carbohydrate daily is recommended for preventing ketosis, but McCracken and Parsons (1958) claim that even this permits protein breakdown in the anuric patient in excess of what would be normal in healthy subjects. They give 100 g. of glucose daily with vitamins in 400 ml. of water by mouth and add additional fluid calculated from the daily weight loss. Efforts are made to adjust this to 300–400 g. They summarize the principles of treatment under two headings:

1. Avoid intake of electrolytes and excess water.
2. Reduce protein metabolism to a minimum.

Norethandrolone

A recent development has been the use of norethandrolone (17α-ethyl-19-nortestosterone) for its powerful anabolic effect on the metabolism of protein. It is available under the trade name of Nilevar and Reference Manual No. 4 (Searle & Co., England) lists references relating to its use. There is doubt whether in uræmia norethandrolone acts as an anabolic agent or restricts catabolism of protein. McCracken and Parsons (1958) claim that protein catabolism is reduced by an average of 70% when the steroid is given to anuric obstetric patients. There was relatively little response in healthy patients on a low protein diet or when failure was due to non-obstetric causes. They considered this was a major advance in treatment and if given early could often avoid the necessity for dialysis. Parsons (1959) stated that a dose of 30 mg. of Nilevar a day given to three obstetric patients with renal failure produced the same restriction of protein catabolism as had 80 mg. in the earlier series. All three patients recovered.

Salivary flow should be stimulated by giving the required nutriment by mouth to lessen drying and cracking of the buccal and pharyngeal mucosa. When coma makes parenteral administration necessary concentrated dextrose solutions can be given into the inferior vena cava. This is not without risk of thrombosis and infection as described by Chambers and Smith (1957) and Bansmer and Keith (1958). An alternative technique using the superior vena cava by threading the catheter through arm veins reduces complications, but whichever route is used meticulous care in avoiding infection is essential.

Immobilization of catheters by suturing and the use of heparin are required to keep complications to a minimum.

Sepsis in Uræmia

Major causes of death in anuric patients were pulmonary œdema, potassium intoxication and uræmic coma. Sepsis became more important when steps were taken to prevent fluid and electrolyte imbalance. Balch *et al.* (1955) found that infection accounted for approximately 45% of deaths in military post-traumatic renal failure and Parsons and McCracken (1959) stated that it was now the chief cause of death in civilian patients. Meroney (1955) pointed out that sepsis could easily be overlooked because of confusion with uræmic symptoms, but when these are due to sepsis they appear earlier in the course of anuria and unless the infection is adequately treated they persist after hæmodialysis. Although it is important to recognize septic shock it is not always present as stated by Ober *et al.* (1956), and Lavery and Dugas and there is then a greater risk of not diagnosing the underlying infection. The early recognition of renal failure and its prompt treatment will speed recovery and in many cases make dialysis unnecessary. When the response to treatment is unsatisfactory, or renal failure is diagnosed too late, dialysis can save life.

Hæmodialysis

The artificial kidney was a major advance. McCracken and Parsons (1959) treated 25 anuric women following obstetrical complications and 17 required hæmodialysis. It was repeated with 2 patients and given three times to another 2 without a death. Four of 19 patients with renal failure of obstetric origin reported by Blagg and Parsons (1960) died. Mortality rates in dialysing units are consistent at about 50%, but less than one-third die when anuria is due to postpartum, postabortal, or nephrotoxic causes. Artificial kidneys have become lower in cost and more readily available, but the best results are obtained by specialist teams treating many patients. These need to be concentrated in centres where the material and facilities are adequate for both treatment and research. In many parts of the world this is not possible and alternative treatment is necessary.

Peritoneal Dialysis

The use of short term intermittent peritoneal dialysis has the advantage of simplicity and infection is no longer the hazard that it was. As the method can be used in isolated areas and can be supervised when necessary by a nurse, much more will be heard of

the contributions it can make. Simple though the procedure is, a more efficient service is possible if anuric patients are concentrated in one place.

The method is based on the work of Putnam (1923) who demonstrated that the peritoneum is an excellent dialysing membrane. In an adult it has an estimated filtering surface of approximately 22,000 sq. cm., which is greater than the area of glomerular filtration in the kidney (Odel *et al.*, 1950). It acts as a semipermeable membrane permitting the passage of water and crystalloids in both directions according to local concentration. It is relatively impermeable to proteins of large molecules. The peritoneal cavity acts as an extension of the extracellular depots of the body and in this way catabolites and soluble poisons can be removed and the volume and electrolyte content of extracellular fluid regulated by peritoneal instillation of appropriate fluids. These must be hypertonic to avoid water absorption and if a solution containing 7%–10% dextrose is used in patients with massive œdema, fluid is removed in excess of the volume injected and œdema is reduced. Solutions of this strength can result in such a rapid transfer of fluid from the vascular compartment into the peritoneal cavity that sudden hypotonia may produce shock. The immediate treatment is to give whole blood, which should always be available when concentrated dialysing solutions are used, and to change to a weaker preparation such as 1.5% dextrose.

Legrain and Merrill (1953) described a simplified technique for continuous transperitoneal dialysis. Since then many publications have illustrated its use in renal failure (Maxwell *et al.*, 1959; Doolan *et al.*, 1959; Askari *et al.*, 1959) and in poisoning by various agents, (Elliot and Crichton, (1960); Segar, (1960); and Stinebaugh, (1960)). Franklin and Merrill (1960) think it is not as good as the artificial kidney but provides a simple readily accessible and effective means of controlling fluid and electrolyte balance as well as nitrogen retention. Lavery and Dugas (personal communication), with a considerable experience of acute renal failure in obstetrics in an institution where an artificial kidney is available, are enthusiastic about peritoneal dialysis as the method of choice for this type of patient. Smith *et al.* (1965) are using it to an increasing extent in the Renal Unit at Hammersmith.

Equipment. Two dialysing fluids (Dianeal) resembling extracellular fluid minus its potassium are supplied by Baxter Laboratories in sterile 1 l. flasks. One contains 1.5% dextrose and the other 7%, the latter being used in patients with gross œdema. Potassium

is omitted because of the rise in serum potassium in these patients, but if dialysis is used for poisoning, potassium chloride can be added to bring the concentration to 4 m. equiv./litre.

For each exchange 2 l., warmed to body temperature, are necessary and 40–50 exchanges are sometimes required extending over several days. Heparin (1,000 units) is added to one flask and 25 mg. of tetracycline to the other. The heparin lessens the risk of coagulation blocking the catheter and can be discontinued after several exchanges if the fluid returns freely. The Y-shaped administration set (Fig. 6) and the peritoneal catheter are supplied as sterile disposable apparatus. A sterile syringe with lignocaine 0·5%–1% and needles suitable for infiltrating the anterior abdominal wall, a knife and a sterile trocar set, through which the peritoneal catheter can be inserted, are required.

The patient should be supine and with aseptic technique the area through which the trocar will be passed—in the midline and approximately one-third of the way from the umbilicus to the symphysis—is anæsthetized down to the level of and including the peritoneum. A small stab incision facilitates passing the trocar, which is inserted into the peritoneal cavity and the cannula is directed towards the right iliac fossa so that the catheter can be passed as far as possible into the pelvis. The two bottles connected to the Y tubing are joined to the catheter and the fluid is run into the peritoneal cavity as rapidly as it will flow, usually taking 5–10 minutes. If the flow is impaired the catheter can be manipulated, the patient turned from one side to the other, the head of the bed raised or lowered, or the plastic chamber squeezed. The tubing is clamped while still full of fluid and the empty bottles are placed on the floor (Fig. 6). The dialysing fluid remains in the peritoneal cavity for $1\frac{1}{2}$ hours, at the end of which time the clamp is opened and the solution drains back into the bottles. This should take about 10 minutes. If drainage is inadequate the catheter can be manipulated or syringed, pressure can be exerted gently on the abdomen, or the position of the patient can be altered. Occasionally a new catheter has to be inserted. Two new warmed flasks connected to a new sterile Y administration set are available so that as soon as drainage is complete the second exchange can begin. The number of exchanges, the time taken for each, the nature of the returning fluid, and the general response of the patient are recorded. When dialysis is continued for several days blood potassium levels are watched and potassium chloride is added to the dialysing fluid when indicated.

FIG. 6. Peritoneal Dialysis.

Peritonitis

Baxter Laboratories state that peritonitis is an absolute contra-indication to peritoneal dialysis, a view shared by Maxwell *et al.* (1959). As a result of their experience with anuria in septic abortion with peritonitis, Lavery and Dugas believe this advice is not correct. No patient developed peritonitis during dialysis, but some with peritoneal infection were dialysed successfully. Pus found when the catheter is inserted is cultured for organisms and sensitivity, but they proceed with dialysis and use chloramphenicol until results are known. The catheter is more liable to block in the presence of a purulent infection, but can be syringed, manipulated, or changed. As many as six changes during one course of treatment in the

presence of infection were necessary. Burns *et al.* (1962) and Thomson *et al.* (1964) share the opinion of Lavery and Dugas. Burns described peritoneal dialysis as:

. . . a safe and effective adjunct to the treatment of the uræmic patient. It should be used early rather than late in the treatment of acute renal failure to prevent, rather than to reverse, the severe manifestation of uræmia. Infection complicating the procedure is rare and bacterial or chemical peritonitis *per se* represents no contra-indication to its use.

An important finding in the septic abortion series reported by Lavery and Dugas was that some patients responded well to dialysis, renal function returned satisfactorily, but death occurred later from recurrent septicæmia. Patients are now observed longer after the acute episode is safely over. Smith *et al.* (1965) reported infection as the cause of death in 8 of 11 patients who developed anuria and died.

Ligation of Vena Cava

Septic thrombo-embolic metastases sometimes occur after abortion with endotoxic shock and anuria. Clinically they resemble postpartum and postabortal anaerobic streptococcal infection before sulpha drugs and antibiotics were introduced. Rigors, high temperatures, and jaundice are common features. Gram negative coliform organisms, staphylococci, and streptococci may be isolated. Aerobic and anaerobic cultures are necessary but these were positive in only 40% of Baragwanath patients and signs of pelvic infection were detected in only 60%. Based on the work of Collins (1946), the inferior vena cava was ligated in 5 selected patients whose condition was deteriorating in spite of treatment. There was one death. Those who seemed moribund were described as "sitting up and looking well a few hours after operation". The response was rapid. Both extraperitoneal and intraperitoneal ligation were tried but the experience was insufficient from which to decide which was better. The procedure is obviously desperate, but in view of the reports from Tulaine and Baragwanath it is worthy of consideration when conservative measures fail.

Pulmonary Embolism

The last of the four major causes of maternal death is pulmonary embolism, the incidence of which has altered relatively little (Table 9). A slight fall in the last triennium occurred in spite of a 13% rise in the number of births. The significance of this, if any, is not yet

understood. The analysis of these deaths teaches no obvious lesson comparable to those applicable to toxæmia, hæmorrhage and abortion. At present 18 % of maternal deaths are due to pulmonary embolism which now ranks equal with toxæmia and abortion as a killer in obstetrics.* There are relatively few in which avoidable factors have been identified and the figures of 6 %, 10 %, and 16 % (Table 15) are offered with considerable reservation because of uncertainty as to the ætiology of the condition. Analysis of avoidable factors in toxæmia, hæmorrhage and abortion has indicated ways of reducing the mortality by approximately half, but this cannot be

Table 15
MATERNAL DEATHS: PULMONARY EMBOLISM.

	No.	Avoidable Factors	Total Births
1952-54	138	6%	2052000
1955-57	157	10%	2149396
1958-60	132	16%	2322229

said of pulmonary embolism and it is reasonable to expect that it will become the most important cause of maternal death. For this reason there is greater need for concentrated research on its ætiology and prevention. The fact that it is an important problem throughout the whole range of medicine and surgery should increase the chance of its solution and makes it the more necessary that reports of progress in one field should be reviewed for possible applications in others.

At the present time the risk of a fatal embolism associated with pregnancy is approximately one in 20,000 deliveries. By comparison, Morrell *et al.* (1964) found the incidence ranged from virtually 0/1,000 hospital inpatients aged 20 and under, to more than 10/1,000 at the age of 60. In a total population of over 200,000 consecutive inpatients (excluding maternity) during the 10-year period 1952–61 in two large hospitals the rate was approximately 2/1,000 at the age of 30 and nearly 5/1,000 at 50. They concluded that age has a profound influence on the liability to embolism. At all ages medical patients had a higher mortality than surgical, and after the age of 30 it became an appreciable risk, increasing steeply with advancing years until by the age of 80 it was over

* In 1961–1963 it was second to abortion as a major cause of maternal mortality and was responsible for 129 deaths.

20/1,000. Study of 853 patients with embolism, of whom 439 died, led the authors to conclude that it "virtually does not occur below the age of 40 in surgical patients and only begins to be frequent after the age of 50". Much depends on what is meant by "virtually does not occur below the age of 40" because fatal embolism occurred in approximately 2/1,000 medical inpatients aged 40 and in 1/1,000 surgical patients of the same age. Compared with corresponding rates of 10/1,000 and 5/1,000 at the age of 60, and nearly 20/1,000 and 10/1,000 at 70, the rate at 40 might conceivably be described as "virtually nil", but it is high compared with the incidence of one in 20,000 deliveries in England and Wales. This indicates the safety of modern obstetrics but raises the interesting question for physicians as well as obstetricians of why the risk is so much lower in the obstetric group. It is possible, if not probable, that an investigation conducted by physicians on the lines of the Maternal Mortality Enquiry would provide the answer. As a fatal complication of Cæsarean section embolism was responsible for one death in every 2,000 operations between 1952–60. Among other information required but not yet available is the significance, if any, of varicose veins, previous thrombosis, anæmia, the relative incidence of non-fatal to fatal pulmonary embolism in obstetrics, and the age incidence. The answers may make it possible to recognize in the antenatal period those patients at greatest risk and take appropriate precautions. Although the risk of death is now only one in 20,000 deliveries and one in 2,000 Cæsarean sections it is probable that in certain categories, as yet undefined, the danger is much greater and that these contribute most of the fatal cases. Morell *et al.*, have established that the risk is increased in the elderly patient and it is probable that further research will define avoidable factors.

Browse (1964) studied the activity of surgical patients and measured with an electromyograph contraction of the calf muscles before and after operation. This decreased immediately after surgery but was back to normal in 24 hours and he concluded that inactivity was more important than operative trauma in the ætiology of thrombosis. If this were proved it would help to explain the surprising facts revealed in the more extensive study of Morrell *et al.* that the risk of embolism is approximately twice as high among medical inpatients than it is after operation. Early ambulation and discharge of obstetric patients may be their safeguard.

In the meantime there are many differing opinions concerning the ætiology of thrombosis and embolism, its prevention and its treatment. Even on the important question of anticoagulant therapy

there are widely divergent views. Nine patients died while on this treatment (1958–60, Walker *et al.*, 1963). Twice it was given prophylactically because of a history of thrombosis and three patients died during anticoagulant treatment after thrombosis occurred, while in the remaining four treatment commenced after a pulmonary embolism. No conclusions can be drawn from this information, and the fact that bleeding was not reported in any of the patients concerned gives rise to doubt as to whether adequate anticoagulant treatment was given. Sevitt and Innes (1964) reviewed the considerable risk of death in patients suffering from a fractured neck of femur and stated that the prolongation of prothrombin time to more than twice normal was necessary to guarantee antithrombic effect in patients susceptible to deep vein thrombosis. This inevitably resulted in an increased hæmorrhage rate, but from an extensive experience of these high risk patients at the Birmingham Accident Hospital Sevitt (1964) stated:

We accept the extra unavoidable hæmorrhages (the great majority are minor and of no importance) in order to save all those at risk from the morbidity of thrombosis and mortality of embolism.

The possibility of rebound hypercoagulability after stopping anticoagulant treatment (Hillman, 1964) is of obvious practical importance and requires further study.

It would seem reasonable to believe that similar principles apply in obstetrics but the fact remains that much more accurate information is necessary concerning the extent to which anticoagulant treatment can be given with safety, and with what results, in the pregnant and puerperal woman. The decision on whether it should be given at all, and if so when, will depend on this information. When patients at greater risk can be defined accurately, active measures to safeguard them will become a practical possibility and pulmonary emboli will no longer be regarded as an act of God and therefore unavoidable. The Ministry of Health has begun a prospective study of fatal embolism in obstetrics. A special form dealing with "Deaths from Pulmonary Embolism" is available to Regional Assessors and will be completed in addition to the one for all maternal deaths. Details are collected on age, family and personal history of thrombosis, general health prior to delivery and in the puerperium, hæmoglobin levels, varicose veins, complications of pregnancy necessitating prolonged rest, volume of blood lost in the third stage, trauma and anæsthesia at delivery, the technique used for the third stage, whether lithotomy poles were used and whether

labour commenced spontaneously or after induction, whether physiotherapy was given and if so to what extent, elevation of temperature and pulse rate in the puerperium, whether anticoagulant treatment was given and if so in what form, for how long and in what dose. If maternal deaths from pulmonary embolism continue even at the present rate it will take 10 years to collect a series comparable with the 439 non-obstetrical deaths reported by Morrell, *et al.* (1964).

Heart Disease in Pregnancy

This caused the death of 289 women (Table 16) and avoidable factors were present in 101 or 35%. The number fell in each triennium and in the last was almost 50% of the first (Walker *et al.*, 1963).

Table 16

MATERNAL DEATHS: HEART DISEASE.

	No.	No. with Avoidable Factors
1952–53	121	40
1955–57	102	40
1958–60	66	21
TOTAL	289	101 (35%)

A gravida 5, aged 44, was known to have valvular disease of the heart. She twice developed toxæmia without cardiac failure and was booked for home confinement. Acute infective endocarditis developed and she died.

A gravida 5, aged 35, known to have heart disease was booked for delivery in a small maternity home. She was abnormally tired in previous pregnancies but no attempt was made to obtain a consultant opinion. She became postmature, labour was induced and she died from cardiac failure.

Four deaths (1963 Report) occurred after cardiac patients failed to keep antenatal appointments.

A para 1, aged 35, with valvular disease was referred to hospital for booking. She attended the antenatal clinic regularly until the 22nd week when she was sent home to rest as it was noted that she was "ill". She failed to report in a week and 5 days later she died.

Summary

Obstetrics demands team work of the highest order. Heart disease in pregnancy is an excellent example of the need for this and imposes a responsibility which the obstetrician should share with a physician. It is not a static condition and the fact that previous pregnancies have been uneventful can give rise to a false sense of security, nor does successful surgical treatment for mitral stenosis justify regarding the heart as normal in subsequent pregnancies. Three mothers of the last 66 who died were in this category. Periods of rest, often essential, should be *controlled in hospital* as a life-saving contribution of antenatal care. Cæsarean section is the most dangerous way to deliver a woman with heart disease and 6 of the 66 deaths (1958–60) occurred during operation. If section is necessary for some other complication the dangerous situation demands the co-operation of physician, anæsthetist, and obstetrician. It is unfair to all concerned to delegate unsupervised responsibility to a specialist in training.

The doctor's responsibility does not end when the mother is safely delivered and ready to return home. Careful planning for her future is of the greatest importance and she should be acquainted with the ways and means provided to help her (Chapter 7).

Anæsthetic Deaths

These are fortunately rare, 110 deaths in over 6,000,000 consecutive deliveries (Table 17). They would be even rarer if the best current practice were more widely adopted, for 60% were due to inhalation of vomit. This causes sudden death or, as happens in about half the cases, Mendelson's syndrome (1946) develops with

Table 17

MATERNAL DEATHS: ANAESTHESIA.

	No.	Inhaled Vomit
1952–54	49	32
1955–57	31	17
1958–60	30	17
TOTAL	110	66 (60%)

acute pulmonary œdema and peripheral failure a few minutes or hours later. Hausmann and Lunt (1955) thought the action of placental hormones on the adrenal cortex might be important in causing this complication. Inhalation can occur during induction, operation, or during recovery from the anæsthetic and no anæsthetized patient should be left unattended until fully conscious. This is a powerful argument in favour of recovery units attached to operating theatres and labour ward suites. Four practical points deserve emphasis:

1. It is never safe to assume in pregnancy or labour that because food has not been taken the stomach is empty.
2. Glucose drinks are dangerous when general anæsthesia is necessary and cause many disasters (Dinnick, 1958).
3. A mask should never be strapped on the face of an anæsthetized patient.
4. The obstetrician should not fill the dual role of anæsthetist and midwife.

Conduction techniques reduce to a minimum the risk of inhalation tragedies, but deaths have been caused by caudal, spinal and even pudendal anæsthesia, the dangers of which should be realized by all who use them. Prevention is the ideal but equipment necessary to deal effectively with acute complications should be available for immediate use. For example, respiratory collapse following spinal or caudal anæsthesia requires intubation, controlled oxygen inflation, and patience not panic. If shock and hypotension are the cause of anxiety, increased oxygen is necessary and the administration of methedrine 30 mg. intramuscularly or intravenously according to the degree of emergency, or aramine (metaraminol bitartrate) 5 mg. as a maximum dose intravenously if the situation is desperate.

In view of the commendable increase in the use of local anæsthesia it should be remembered that lignocaine is more powerful than earlier preparations and 0.5% with $1/200,000-1/300,000$ adrenaline is all that is necessary for infiltration or pudendal block. A maximum dose of 500 mg. should not be exceeded and even this should seldom be required. The injection of 50–70 ml. is usually more than adequate. If convulsions develop a recent advance is to curarize the patient, pass an endotracheal tube and control respiration with adequate oxygen intake. This technique, described by James and Whitty (1961) in the control of status epilepticus in pregnancy, is valuable

for convulsions due to tetanus, poisons, and even status eclampticus not responding to more conventional therapy.

Walker *et al.* (1960) state:

Many of these tragedies could have been avoided by a more experienced anæsthetist. . . . A consultant should be responsible for anæsthetics in the obstetric department, for the instruction of his juniors, and should be available for consultation by them in any case of difficulty.
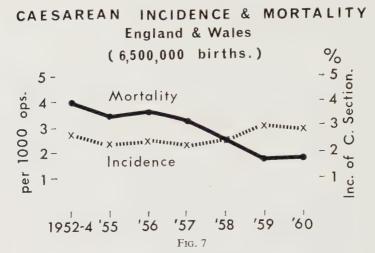
This official declaration of policy is welcome at a time when the Health Service is under review. In a few areas (Portsmouth is an outstanding example (Hodges and Tunstall, 1961)) the concept has been translated into practice. Its wider acceptance would be a major advance in obstetrics. The criteria for an ideal obstetric anæsthetic service were defined by Hodges (1963) as follows:

1. Protection from vomiting and regurgitation.
2. Provision of supportive therapy.
3. Avoidance of maternal hypotension.
4. Avoidance of maternal respiratory depression.
5. Increased oxygenation.
6. Avoidance of fœtal respiratory depression.
7. Provision of neonatal resuscitation.
8. Provision of a 24-hour service.

Cæsarean Section

No surgical technique requires more constant reappraisal than section, for when an operation is proclaimed safe it can become dangerous. The more dramatic its appeal the greater the danger.

Certain indications for operation are generally accepted such as major degrees of placenta prævia, while others, such as the mode of delivery of a diabetic woman, vary according to the obstetrician (Chapter 5). A vaginal delivery which would be safe in one set of circumstances would be dangerous in another and the experience of the obstetrician and the facilities available are major factors in deciding this. With the increasing use of section the assumption that it is a safe operation leads many into trouble. Surgery can replace obstetric judgement and the risks involved are worthy of attention. They have been studied critically with assessment of avoidable factors in 497 deaths (1952–60) in an estimated number of 117,232 sections representing approximately 2% of all births. The mortality was $4/1,000$ operations, but was later halved to $2/1,000$

CAESAREAN INCIDENCE & MORTALITY
England & Wales
(6,500,000 births.)

Fig. 7

(Fig. 7). This is seven times the national figure for all births. The following five guiding principles may be useful:

1. Cæsarean section is *not* always a safe operation.
2. General conclusions drawn from a small experience can be dangerous.
3. Mortality and morbidity are directly related to the experience of the surgeon and the facilities with which he works.
4. Some obstetrical complications are best treated by Cæsarean section, while others are less dangerous when treated conservatively.
5. The heresy of yesterday sometimes becomes the accepted procedure for tomorrow.

Because of the favourable conditions under which most surgeons now work and the innate urge to live which most patients possess, it is possible to do the wrong thing repeatedly without the death penalty being exacted. With a small experience this can lead to the false assumption that a procedure is safe. The list of maternal deaths includes the names of many who gained entry in this way. The three Reports of Walker *et al.* are salutary volumes of reference available for study by the most junior surgeon on the eve of performing his first section. Readiness to profit by the mistakes of others is a key which unlocks the gate to the path of wisdom. The

tragic correlation of inexperience and high mortality is illustrated repeatedly and risks increase with inadequate facilities.

A gravida 8, aged over 40, with a history of Cæsarean section was admitted with antepartum bleeding to a small maternity home. Her condition was described as poor, no blood was available, but emergency section was performed. She died.

The potentially fatal significance of poor condition due to hæmorrhage or exhaustion was either not realized or ignored in 60% of women who died after being booked for delivery at home or in a small maternity unit. They are important avoidable factors. There is a difference between experience and training. A task performed 100 times provides considerable experience even if the standard of work is poor. To complete the same procedure only once or twice with the necessary guidance to ensure that it is done well establishes a basis from which to develop high standards. Deaths occurring in hospitals with experienced senior staff, none of whom is present during the emergency, are even more tragic. The fact that 166 (33%) of all Cæsarean deaths were attributed to hæmorrhage and shock is grim. There are well defined categories of high risk patients for section and it is unjustifiable to entrust the unsupervised responsibility for them to surgeons in training when senior colleagues are available to assist. With the application of these principles Pillsbury (1963) was able to report 2,316 consecutive Cæsarean sections without a maternal death. In a personal communication the number had risen to 2,575 by March 1964.

High Risk Patients

These include the following eight categories:

1. Those who are exhausted, ketotic, and possibly already infected after prolonged labour.

2. Those who have had unsuccessful attempts at vaginal delivery.

Note: These two groups were recognized as particularly dangerous by surgeons in the nineteenth century. There is no excuse for forgetting the risks today.

3. Those with associated diseases, particularly cardiac lesions.
4. Those with serious antepartum hæmorrhage or anæmia.
5. Those with suspected major degrees of placenta prævia with or without hæmorrhage.
6. Those with obstructed labour.
7. Those requiring repeat Cæsarean section, particularly if there is a possibility of ruptured scar.
8. Those with fibroids.

The details of many Cæsarean deaths suggest that the increased hazards of operating on high risk patients have not been realized and necessary precautions have not been taken. Others emphasize the importance of avoidable factors common to deaths from all causes, including wrong booking, inadequate antenatal care with particular reference to neglect of general health, anæmia, and associated diseases, and confusion of responsibility with at times its delegation to those not adequately trained to accept it.

All patients in the groups summarized above require the highest standard of care from the time of the first antenatal visit. To make this possible it is essential that the number who book late in pregnancy should be reduced to a minimum. Acheson (1964) in his record linkage study of a population of approximately 235,000 found that of 1,600 women who had their babies at home no fewer than 278 (17%) were seen for the first time by a midwife between the 30th–39th week of pregnancy (personal communication). This was the more disquieting in that it happened in a region with a low maternal mortality. There is urgent need for better public education on the importance to mother and baby of early efficient antenatal care.

Over 50% of deaths were due to hæmorrhage, shock, sepsis and anæsthetic complications.

A gravida 11 was booked for home delivery. Labour began with a transverse lie which was recognized after considerable delay. A Flying Squad was not summoned and there was further delay before admission to hospital. She died during Cæsarean section.

The error is not always made at home or in a general practitioner unit.

A young primigravida had a difficult forceps delivery. An impacted shoulder with a dead infant was diagnosed during labour in hospital with her second. Death occurred from hæmorrhage during Ceasarean section.

The 1963 Report included 10 deaths from obstructed labour in hospital patients, in 7 of whom there were repeated attempts at forceps delivery, with rupture of the uterus in 5 and in 2 the mother died during operative delivery of a stillborn infant. The failed forceps patient is in the high risk category and her safe care demands supervision by the most experienced staff available.

Hæmorrhage and Shock

These accounted for 33% (166 in 497) of all Cæsarean deaths between 1952–60 (Table 18), while in 1958–60 they were the immediate cause of death in 57 of 130 fatal operations (44%) and in 32 out

Table 18

CAESAREAN SECTION, 1952-60.

Causes of Maternal Deaths.

Complication	1952-54	'55-57	'58-60	Total
HAEMORRHAGE & SHOCK	65	44	57	166
PULMONARY EMBOLISM	32	33	27	92
SEPSIS & ILEUS	26	30	23	79
ANAESTHETIC	12	11	5	28
HEART DISEASE	6	15	3	24
MISCELLANEOUS	42	51	15	108
TOTALS	183	184	130	497

N.B.   146 or 30% had Avoidable Factors.

of 41 with avoidable factors (80%). There are occasional exceptions to any general rule, but the ideal that no obstetric patient should die from hæmorrhage is not unattainable. If it were generally achieved Cæsarean deaths would be reduced by one-third on this count alone and there is evidence to show how it could be done. Two important lessons are:

1. The volume of blood lost at operation is usually greater than appreciated.
2. The pre-operative preparation for section is sometimes more important than the technique of operation. It should begin at the first antenatal visit.

The lethal contribution of pre-operative anæmia to the effect of hæmorrhage is often overlooked. The better the sucker and the assistant the greater the danger of assessing optimistically the amount of hæmorrhage. It is easy to regard fluid in the suction bottle as being mainly liquor when in fact it is blood. Wilcox *et al.* (1959) found the average blood loss in 25 Cæsarean sections was 1,028 ml. and the maximum was 3,180 ml. They concluded that it was impossible to guess with accuracy the quantity of blood lost at

operation, and surgical experience was one of the most important factors in maintaining a minimal amount of bleeding. Practical implications are that whenever possible section should not be performed on a high risk patient by an inexperienced surgeon, and blood should always be available in the theatre before the operation begins.

Study of avoidable factors reveals repeatedly that little attention was paid to the general health of patients. The blood group, rhesus factor, and hæmoglobin estimations were often not determined and if anæmia was found it was not treated. Blood was often not available at emergency section and the operation began with the patient in poor condition and with inadequate facilities. Avoidable factors were sometimes multiple, beginning in the antenatal clinic and continuing into the theatre. Four guiding principles can be a comfort in emergency:

1. There is no hæmorrhage which cannot be controlled by pressure.
2. The uterus at section is readily accessible for uterine artery compression if this is needed.
3. Oxytocics and patience are important during operation.
4. The more shocked the patient, the less anæsthetic is required and the greater the chance of uterine atony with further bleeding.

Major disasters such as shipwreck or fire at sea reveal the necessity for disciplined action to avoid panic and loss of life. It is too late to wait for the emergency before testing equipment and deciding on what action must be taken in a rapidly changing scene. In the same way the surgeon must always be in control of the situation in the theatre, know the hazards to be faced, how to avoid them when possible, and what to do in the moment of crisis. There will always be the first time in a surgeon's experience when he faces imminent disaster to his patient, but that is not the moment for wondering what to do, while futile efforts add to confusion.

When the head is delivered at section, ergometrine or its equivalent should be given intravenously by the anæsthetist, by prior arrangement, and the infant's airways cleared in less than the minute it takes to work. As the uterus contracts delivery is completed slowly and by waiting a minute or two before removing the placenta bleeding will be reduced to a minimum. In this way the technique resembles closely the modern method of slow delivery of the infant in a vaginal delivery followed by active intervention in the third stage.

Uterine Inertia

There were 50 deaths associated with section for uterine inertia (1955–60). Hæmorrhage, embolism, sepsis and ileus were the common causes with hæmorrhage a particular hazard. In 37 patients inertia followed induction of labour. A Ministry Enquiry in 1959 disclosed that $11\cdot3\%$ of women in the maternity units investigated were induced surgically and $27\cdot8\%$ of Cæsarean sections were performed for inertia following this. The potential fatal sequence of induction/inertia/section/death should be kept constantly in mind by all who practise obstetrics. Oxytocic infusions have reduced the incidence of failed induction but have not eliminated the sequence of induction and inertia. This is particularly liable to happen with primigravidæ, large babies, and the posterior position. Dilatation of the bowel, which may be rapid in onset, and progressive œdema of the undilating cervix are two important indications that delivery should be effected without further delay. Mortality is increased by dehydration, exhaustion and ketosis and these should be treated before operation. Dilatation of the stomach increases the risk of general anæsthesia. For these reasons the most experienced staff available should accept responsibility not only for deciding that operation is necessary but for performing it and anæsthetizing the patient.

Fields and Welling (1963) reduced the section rate from 4% in 1949 to $2\cdot6\%$ in 1959 at Pennsylvania University by progressively increasing use of intravenous oxytocin and caudal anæsthesia. The major indications for section were little changed whereas the order of frequency was. More were performed in the fœtal interest and fewer for inertia, toxæmia and medical complications of pregnancy. These results emphasize the statement made at the outset that the role of Cæsarean section in modern obstetrics needs constant reappraisal.

Repeat Section

Deaths were recorded when repeat Cæsarean sections presented difficulty because of adhesions. For this reason the patient requiring repeat section is in the dangerous category. When there is reason to doubt the strength of a uterine scar following section, a useful technique is to study the uterine cavity by hysterography before a subsequent pregnancy begins, as described by Poidevin (1958).

Symphysiotomy

Alternative methods of delivery are possibly more important in areas such as Africa than in Britain. When it can be assumed that after section a woman will report for skilled supervision in subsequent pregnancies there will be less difficulty in deciding to perform the first operation. Where the chances of the patient failing to report are considerable, the role of symphysiotomy as described by Spain (1949), Zarate (1955) and Seedat and Crichton (1962) must be considered as an alternative when the indication is cephalopelvic disproportion.

Vacuum Extractor

The vacuum extractor was discussed in the last edition of this book. It can play an important part in reducing the incidence of Cæsarean section as described by Chalmers and Fothergill (1960), Lasbrey and Crichton (1964) and others, but the dangers associated with prolonged extraction should be remembered. Lasbrey and Crichton found that the incidence of fœtal cerebral trauma could be correlated with the amount of traction. They studied 403 infants delivered in this way and brain damage was diagnosed in $4\cdot4\%$ early in the series (1961) and in $1\cdot5\%$ in 1962 and 1963. The incidence was 1% in the second series when fewer than six pulls were necessary and 5% when more were required.

Elderly Primigravida

Jacobson (1963) studied the obstetric prognosis for primigravidæ aged 35 and over and stressed the contribution which Cæsarean section could make in reducing both maternal and perinatal mortality and morbidity. He found complications of pregnancy or delivery in approximately 66% of women in this age group and high or mid forceps carried a 9% infant death rate. Low forceps were much safer, but when section was performed, or the ventouse applied, deaths were few. In a series of 543 primigravidæ with a minimum age of 35 the number of infants delivered was 550. Cæsarean section was performed 97 times (18%), and the ventouse applied 10 times ($1\cdot8\%$) with no perinatal deaths. Forceps were applied 120 times ($21\cdot8\%$) and there were 316 women who delivered themselves spontaneously. There was a total of 24 perinatal deaths, an incidence of $43\cdot6/1,000$ births, but as these all occurred following spontaneous delivery or forceps it meant that the mortality in these

two groups combined was approximately 54/1,000 births. This is a high figure, and particularly so for women pregnant for the first time and approaching the end of their childbearing life. It supports the claim for a more generous use of section in the treatment of the elderly primigravida who is not obstetrically normal.

Infection

Only 112 deaths from infection in over $6\frac{1}{2}$ million deliveries would have been unbelievable earlier this century. It throws into more tragic relief the 324 deaths from septic abortion certified by the Registrar-General during the period of the Enquiry. Infection was also responsible for 16% of Cæsarean deaths and the danger was particularly great when operation was performed for inertia. In 1906 Frank demonstrated the value of protecting the peritoneal cavity from infected liquor and blood at a time when peritonitis had a high mortality. Today there is sometimes carelessness in regard to this precaution and some surgeons make no effort to avoid soiling the peritoneal cavity, perhaps subconsciously relying on antibiotic rescue if infection follows. It is not always effective. The use of a Macfarlane roll is commended. Moistened with warm saline it is packed gently between the unopened uterus and the parietal peritoneum while the abdominal wall is elevated with a retractor so as to cause minimal peritoneal trauma during its insertion. One roll is adequate and removes the danger of leaving a swab inside (Chapter 9). When infection is suspected it is wise to make aerobic and anaerobic cultures and sensitivity tests. The lower segment operation proved its ability to reduce peritonitis and ileus to a minimum before the days of chemotherapy and is now safer than ever. It is good to have an efficient technique applicable with maximum safety to the infected patient but much better to reduce to a minimum the incidence of this class of case.

Summary

Ample evidence has been presented to justify the claim that the Confidential Enquiry into Maternal Deaths has resulted in major advances in obstetrics. It was boldly conceived and executed. It has demonstrated most forcibly the requirements of antenatal care. It has indicated those patients at greater risk from varying complications of pregnancy. It has emphasized the importance of recognizing avoidable factors and has demonstrated ways of avoiding them.

Assessed by the reduction in maternal mortality and improved standards of obstetric care it has been an outstanding success, and both in concept and practice provides a challenge which other fields of medicine could do well to accept.

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PERINATAL MORTALITY

The National Birthday Trust Fund initiated and planned a study of the factors which in the prenatal period, and during labour, might have an effect upon early death or abnormality of the baby. For this purpose the Steering Committee of the Perinatal Mortality Survey, under the chairmanship of Miss Josephine Barnes, was established to study all births that occurred between the 3rd and 9th March 1958.

There is some difference of opinion regarding the exact definition of neonatal death and, for the purpose of this chapter, it means death within seven days of birth. The perinatal death rate measures the total number of stillbirths and neonatal deaths (as defined above) per thousand total births. It is comparatively easy to produce a list of the causes of both stillbirth and neonatal death, and such a list may be of great assistance in the study of perinatal mortality, but the Survey gives much information in great detail, thus permitting a more critical examination of the aetiology of fœtal and infant death and of the relevant avoidable factors.

The maternity services have improved since these figures were collected in 1958 and the perinatal mortality for England and Wales has fallen from 35·1 per thousand in 1958 to 29·3 per thousand in 1963. Lessons which can be learnt from the survey are of great importance in effecting further improvements.

Perinatal mortality is expressed in the survey as a ratio known as the Mortality Ratio, which is calculated by taking the average mortality for a particular group and labelling it one hundred. Each subdivision of the total group is related to this average. It will be seen that the mortality ratio for South Eastern England is considerably lower than that of Western England, Wales and Scotland (Table 19).

REGIONAL INCIDENCE OF MORTALITY RATIO

East and West Riding	94	South-Western	105
North Midland	95	Wales	113
Eastern	81	Midland	110
London and South-Eastern	90	North-Western	112
Southern	86	Northern	108
		Scotland	110

Table 19

FIGURE OF REGIONAL INCIDENCE OF MORTALITY RATIOS

When all the perinatal deaths are related to the gravidity of the mother, it is seen that the gravida 1 has a mortality ratio of 106 and that the ratio falls to 74 in the gravida 2. In the gravida 3, however, it climbs to 99 and in the gravida 4 the mortality ratio is 112. The mortality ratio then climbs with gravidity until at 9 or over it has reached 310. It would seem from these figures that all patients having their fourth child should be in hospital, because the apparent risk to the baby in the fourth pregnancy is greater than in the first pregnancy, both of which are, of course, in excess of the second and third pregnancies (Table 20). In a further breakdown of the figures for gravidity in various regions, it is noticed that the mortality in some areas is greater for a woman having her third child than when she has her first baby. These areas are the East and West Riding of Yorkshire, North Midland, London and South-Eastern, Southern and South-Western, with the obvious conclusions that in these areas any woman having her third child is a greater risk than when she has her first baby. Indeed, there is another interesting conclusion to be drawn from these figures, that in the remaining seven areas the mortality ratio for a woman having her third child is no higher than that in the five areas already stated, but in these seven areas the mortality ratio of a gravida 3 is less than that of a woman having her first child because of the comparative increase in the mortality ratio, in these areas, of a woman having her first baby. It would seem, therefore, that particular care must be paid to the primigravida in the following regions (North-Western, Northern, Eastern, Wales, Midland and Scotland), since it is in these areas that the mortality ratio of a primigravida is greater than that of a gravida 3.

A study of the distribution of the mortality ratio within social classes shows that it rises as social class descends. In class I it is 69 and rises to 128 in Class V.

Class I	Professional	69
Class II	Supervisory	80
Class III	Skilled	96
Class IV	Semi-skilled	108
Class V	Unskilled	128

A study of the distribution of the social class within the regions already mentioned, shows that some of the difference in the mortality ratio within the regions is due to heavy weighting within the North-West region, as compared with London and the South-East, by

Table 20

DISTRIBUTION OF POPULATION (P) AND DEATHS (D) BY MATERNAL AGE AND
PARITY WITH MORTALITY RATIO (M)

MATERNAL AGE GROUPS		PARITY					TOTAL
		0	1	2	3	4+	
UNDER 20	P	841	132	5	–	–	978
	%	5.0	0.8	–	–	–	5.8
	D	374	·56	8	–	–	438
	%	5.2	0.8	0.1	–	–	6.1
	M	106	101	382	–	–	107
20 – 24	P	2778	1564	438	111	38	4929
	%	16.3	9.3	2.6	0.6	0.2	29.0
	D	1136	454	142	39	16	1787
	%	16.0	6.4	2.0	0.5	0.2	25.1
	M	98	69	77	84	101	87
25 – 29	P	1791	2025	944	400	290	5451*
	%	10.5	11.9	5.6	2.4	1.7	32.1
	D	750.	529	361	164	154	1959*
	%	10.5	7.4	5.1	2.3	2.2	27.5
	M	100	62	91	98	127	86
30 – 34.	P	621	1062	764	465	509	3422*
	%	3.7	6.2	4.5	2.7	3.0	20.1
	D	343	344	327	216	298	1528
	%	4.9	4.8	4.6	3.0	4.2	21.5
	M	132	77	102	111	140	107
35 – 39	P	208	364	412	281	489	1754
	%	1.2	2.1	2.4	1.7	2.9	10.3
	D	146	183	187	151	333	1001*
	%	2.1	2.6	2.5	2.2	4.7	14.1
	M	168	120	108	128	163	136
40 – 44	P	37	64	77	67	172	417
	%	0.2	0.4	0.4	0.4	1.0	2.4
	D	33	48	71	44	154	350
	%	0.4	0.7	1.0	0.6	2.2	4.9
	M	213	179	220	157	214	200
45+	P	3	2	8	2	17	32
	%	–	–	0.1	–	0.1	0.2
	D	2	2	4	6	20	34
	%	–	–	0.1	0.1	0.3	0.5
	M	159	239	119	716	281	254
NO INFORMATION	P	5	2	3	–	1	11
	%	0.1	–	–	–	–	0.1
	D	9	3	4	2	1	20*
	%	0.1	0.1	0.1	–	–	0.3
	M	430	358	318	–	239	434
TOTAL	P	6284	5215	2651	1326	1516	16994*
	%	37.0	30.7	15.6	7.8	8.9	100.0
	D	2793	1619	1104	622	976	7117*
	%	39.2	22.8	15.5	8.7	13.8	100.0
	M	106	74	99	112	154	100

* These totals include cases of Parity not known
(2 in population : 3 in deaths)

social classes IV and V, which of course carry the highest mortality ratio. This variation of social class by region accounts for some, but not all, of the regional variation in perinatal mortality. This is more easily understood when it is appreciated that social classes IV and V contain more grand multiparæ than social classes I and II. As has already been pointed out a rise in parity increases the perinatal loss.

A total of 4% of births in the survey were illegitimate. The survey mortality ratio in illegitimate children was 159, indicating that the risk to the illegitimate baby is approximately 60% greater than in the remainder of the population.

A study of the maternal age and parity associated with perinatal mortality indicates the importance of both these factors. If we accept a mortality ratio of 100 as being satisfactory, and this after all is the average, then we find that all patients under the age of 20 have a mortality ratio in excess of this regardless of their parity, and indeed amongst the highest risk group of all is a patient under the age of 20 having her third child. In patients between 20 and 24 the mortality ratio remains below 100 until the fifth child, and in patients between 25 and 29 the first child has a mortality ratio of 100 and the ratio then drops below 100 until the fifth child, when it rises to 127. In all patients over the age of 30 the mortality ratio is in excess of 100, with the exception of patients between the ages of 30 and 34 having their second child (Table 21). A patient of 36 having her second child has the same mortality ratio as a patient of 28 having her fifth child. If these figures are to be accepted then the lowest risk patients are those between the age of 20 to 24 having their first, second, third and fourth child, those between the age of 25 to 29 having their second, third and fourth child and those between the age of 30 to 34 having their second child. Patients under the age of 20 fall into a comparatively high risk group, as do all patients over the age of 35 regardless of their parity. The hazard presented by a patient over the age of 40 is very high indeed. It is obvious that no mother falling into such a high risk category should be confined without the benefit of full specialist and hospital facilities.

It is perhaps here of interest to re-examine the lower risk groups to find that these consist of primigravidæ between the ages of 20 and 24; women having their second child between the ages of 20 to 34; women having their third and fourth children between the ages of 20 to 29. All other women fall into a comparatively high risk category, which as stated above rises very sharply after the age of 35.

Just as the mortality ratio rises as parity increases and social class descends, so with each parity group the mortality ratio rises with the descending social class (Table 21).

It will be seen from the above figures that all patients in social class V and all high parity mothers should be provided with the best available obstetric care, as both groups have a particularly high risk and are reluctant to accept hospital treatment. It is possible in this way to estimate the number of high risk patients requiring maximum attention during pregnancy and delivery which means consultant responsibility (direct or delegated) for antenatal care and delivery in hospital.

The number of patients requiring such maximum attention will vary according to the standard that is set (Table 22). If a projected mortality ratio of 70 is to be achieved (that is 70% of the figure obtained by the Perinatal Mortality Survey in 1958, which is surely a reasonable figure to attempt to attain) then consultant hospital care must be provided for 80% of mothers.

It is easy to accept these figures at their face value, but there are a number of factors which have not been taken into account in the

Table 21

MORTALITY RATIOS BY AGE AND SOCIAL CLASS

Social Class	Age Groups					
	20–24	25–29	30–34	35–39	40+	All
1+2	72	62	80	117	126	77
3	83	81	107	130	199	95
4	88	105	114	130	230	108
5	105	114	133	183	268	128
All	87	86	107	136	204	100

Table 22

PERCENTAGE OF MOTHERS IN LOW RISK CATEGORIES BY PROJECTED
MORTALITY STANDARD AND SOCIAL CLASS

Projected Mortality Ratio Standard	Social Class				
	1+2	3	4	5	All
Under 70	6·6	12·4	1·3	0	20·3
Under 80	9·6	16·0	2·5	0	28·1
Under 90	13·1	17·1	2·5	1·7	35·0

survey report. Do the mothers of social class V fall into a particularly high risk category not because they are social class V but because they do not avail themselves of the facilities that are available? There is not much point in removing a relatively low risk patient from good obstetric care in order to make room for a higher risk patient from a lower grade environment when the very reason for the low risk in the first patient is because she is being provided with better obstetric care. The survey does not tell us how many of the patients in social class V fall into a high risk group because they were domicillary confinements. Is there any real advantage to be gained by admitting all such people to hospital, if such admission means refusing patients in other social classes who may then, for this very reason, fall into a higher risk category?

It is perhaps too sweeping a generalization to suggest that admission for hospital confinement should be judged solely upon maternal age, parity and social class, but if these criteria are accepted, then on these criteria alone approximately 20% of patients are suitable for home confinement. This number will be further reduced on account of selective booking within this group for both social and obstetric reasons. The economics of providing a domicillary obstetric service for something considerably less than 20% of mothers must be considered seriously. It would seem as though the domicillary obstetric service is fighting a losing battle, because as the weight of evidence is gradually accumulated it indicates with monotonous regularity the advantages of hospital consultant obstetric care in one group after another.

It seems that the old aphorism "Beware the patient who has previously demonstrated her ability to destroy a child by whatever method" still has some truth and statistical support. There is a significantly higher mortality at each parity for any mother who has a past history of an abortion or ectopic gestation. Any patient who has a past history of one or more abortions should be regarded as a potentially high risk patient and should be booked for hospital confinement (Table 23).

The perinatal mortality in women having second babies is approximately $2\frac{1}{2}$ times greater if she has had a previous premature live born infant, and there is no doubt that any such patient should be booked for hospital delivery.

But even more dramatic is the rise in perinatal mortality in patients who had stillbirths or neonatal deaths. With a second child the mortality ratio is approximately three times that of a patient whose first pregnancy was normal. Such a history is obviously an indication for hospital delivery under consultant supervision (Table 24).

Table 23

THE PERCENTAGE INCIDENCE AND MORTALITY (M) BY PARITY
ACCORDING TO A PAST HISTORY OF ABORTIONS
OR ECTOPIC GESTATIONS

Obstetric History	Parity									
	0		1		2		3		4	
	%	M	%	M	%	M	%	M	%	M
No abortions . .	92	104	89·1	69	85·3	91	83	103	79·7	129
Previous abortions or ectopics . .	8	127	10·9	116	14·7	150	17	155	20·3	173

Table 24

THE PERCENTAGE INCIDENCE AND MORTALITY (M) BY PARITY
ACCORDING TO ONE OR MORE PREVIOUS STILLBIRTHS
OR NEONATAL DEATHS

Obstetric History	Parity							
	1		2		3		4	
	%	M	%	M	%	M	%	M
No previous stillbirths or neonatal deaths	92·2	69	89·3	88	87·1	96	83	116
Previous stillbirths or neonatal deaths	3·8	202	10·7	192	12·9	222	17	245

A past history of pre-eclamptic toxæmia, antepartum hæmorrhage or Cæsarean section also results in a rise in the perinatal mortality, regardless of the parity of the mother, and all such factors are an absolute indication for hospital delivery under consultant super-vision. The majority of people are under the impression that a past history of pre-eclamptic toxæmia is less dangerous as parity increases, but the survey report indicates that the opposite is in fact true.

Place of Delivery and Antenatal Care

Place of Delivery

All Hospital Births	49·1 % (including 8·2 % unbooked and transferred)
All Home Births	36·1 % (including 1·4 % unbooked)
All General Practitioner Unit Births	12·4 % (including 0·8 % unbooked)
All Residual Births (including private)	2·4 %

It is important to note that the Perinatal Mortality Survey classifies general practitioner units separately from hospital units, which shows that only half the total patients are in fact delivered in consultant hospital units (Table 25).

In fact, 40·9% of mothers were booked and delivered in hospitals under consultant supervision and this group suffered from a mortality ratio of 103, which is not significantly different from the national overall mortality ratio of 100. If the antenatal care of those patients booked and delivered in hospital is shared with other services, then the mortality ratio rises slightly. This rise is probably more significant because presumably most hospital consultant units do not share the responsibility of antenatal care for any of their particularly high risk patients. Hospital booked cases whose antenatal care is conducted elsewhere throughout the whole of pregnancy have a significantly higher mortality.

Of mothers booked and delivered at home (34·7% of all deliveries) there is a mortality ratio of 49, which is just under half the national average but usually such women are chosen for delivery under circumstances with minimal facilities because of their low risk. A particularly high risk group is those who are booked for home but transferred to hospital either late in pregnancy or during labour. Five and a half per cent of all mothers fall into this group and have a high mortality ratio of 336. They account for 17·1% of the survey stillbirths and neonatal deaths. Obviously such a high risk group should be eliminated and more careful selection in early pregnancy would help to reduce the risk to these particular patients. The overall perinatal mortality for those mothers originally booked at home regardless of their final place of delivery is 88.

The percentage of mothers booked and delivered in general practitioner units is 11·6, having a mortality ratio of 55, but 1·6% of mothers are transferred from general practitioner units to hospital for delivery and this group, having a mortality ratio of 316, accounts for 5·2% of the perinatal deaths. All general practitioner unit bookings account for 13·2% of mothers and have a mortality ratio of 88.

Unbooked patients delivered in hospital have a mortality ratio of 501, and unbooked mothers delivered at home have a mortality ratio of 482.

An examination of the distribution of the place of booking and the parity of the patient shows that 56·5% of nulliparæ are booked for hospital but that the percentage of hospital confinements then falls with rising parity and that only 24·7% of women having their

Table 25

DISTRIBUTION OF THE POPULATION AND DEATHS BY PLACE OF BOOKING, DELIVERY AND PRENATAL CARE WITH MORTALITY RATIO (M)

BOOKING AND DELIVERY	PRENATAL CARE	POPULATION NO:	POPULATION %	DEATHS NO:	DEATHS %	SURVEY MORTALITY RATIO (M)
HOSPITAL	Hosp only	3143	18.5	1303	18.3	99
	Hosp in part	3088	18.2	1340	18.8	104
	Other only	713	4.2	339	4.8	114
	TOTAL	6944	40.9	2982	41.9	103
HOME	Hosp only or in part	441	2.6	107	1.5	58
	LHA $\pm$ other	2276	13.4	410	5.8	43
	G.P. only	244	1.4	91	1.3	89
	G.P.+Midwife	2922	17.2	602	8.5	49
	TOTAL (INCL. RESIDUE)	5901	34.7	1216	17.1	49
Home Hospital Transfers		935	5.5	1317	18.5	336
ALL HOME BOOKINGS		6836	40.2	2533	35.6	88
G.P.U.	Hosp only or in part	882	5.2	206	2.9	56
	LHA $\pm$ other	191	1.1	40	0.6	50
	G.P. only	828	4.9	186	2.6	54
	G.P.+ Midwife	65	0.4	19	0.3	70
	TOTAL (INCL. RESIDUE)	1973	11.6	458	6.4	55
G.P.U. Hospital Transfers		277	1.6	367	5.2	316
ALL G.P.U. BOOKINGS		2250	13.2	825	11.6	88
Unbooked Hospital		133	0.8	279	3.9	501
Unbooked Home		61	0.4	123	1.7	482
Other Hospital *		44	0.3	60	0.8	326
Other Home *		175	1.0	121	1.7	165
Other G.P.U. *		141	0.8	58	0.8	98
Del. Ambulance Taxi Street etc		17	0.1	42	0.6	590
Private Nursing Home		393	2.3	94	1.3	57
ALL HOSPITAL BIRTHS		8333	49.1	5005	70.3	143
ALL HOME BIRTHS		6137	36.1	1460	20.5	57
ALL G.P.U. BIRTHS		2114	12.4	516	7.3	58
ALL RESIDUAL BIRTHS		410	2.4	136	1.9	79
TOTAL BIRTHS		16994	100.0	7117	100.0	100

* On subsequent tables these groups appear within "ALL BIRTHS" totals only

fourth child, and 29% of women having their fifth or subsequent child are in hospital. This latter group falls into a very high risk category, having a mortality ratio of 154. Such a state of affairs is obviously most unsatisfactory. Bookings for home confinement obviously follow an opposite pattern with 19·8% of nulliparæ booked for home and the percentage then rising until a figure of 60% is reached for all women having their fifth and subsequent child (Table 26).

Table 26

PERCENTAGE OF PATIENTS BOOKED FOR HOSPITAL DELIVERY
BY PARITY WITH OVERALL MORTALITY (M) BY PARITY

Place of Booking	Parity					
	0	1	2	3	4+	All
Hospital booked	56·5	35·2	29·8	24·7	29·0	40·9
Home booked	19·8	46·0	54·8	62·4	60·0	40·2
G.P.U. booked	17·9	12·8	9·6	9·1	5·5	13·2
Overall mortality ratio (M.) . .	106	74	99	112	154	100

Fifteen per cent of nulliparæ are booked for general practitioner units, but the percentage gradually falls with rising parity until a figure of 5% is reached for patients having their fifth and subsequent child.

The mortality ratio in patients who are transferred from home and general practitioner units to hospital is more than three times the national average and, as such, merits further study. Twenty-three per cent of all primigravidæ booked to have their baby at home have to be transferred either in late pregnancy or during labour, and as these patients suffer a mortality ratio of 266 (compared with the national average of 100) there is surely very little excuse for any woman having her first child at home. Fifteen per cent of patients having their fifth and subsequent child are transferred from home to hospital and such patients have a mortality ratio of 422. Similarly, 9·5% of grand multiparæ are transferred from general practitioner units to hospital and have a mortality ratio of 627. The higher mortality in this group of grand multiparæ may be because in such patients there is less time for emergency transfer when trouble develops. This is also a lesson learned from the Maternal Mortality Enquiry (Chapter 1).

The above figure makes it abundantly obvious that greater care has to be exercised in the selection of patients for confinement both in the home and in general practitioner units, which means, in fact and in effect, that a greater percentage of patients must both attend hospital clinics and be delivered in hospital.

The group with the lowest mortality ratio consists of patients having their second babies at home. This suggests that there is an effective filter at work which presumably removes most of those patients who had abnormalities in their first pregnancy, but even this figure could be further reduced by greater selectivity in the choice of patients for home confinement.

The percentage selection for home delivery rises with the lower social class partly due to a concomitant reduction in both hospital and general practitioner unit bookings. This may, of course, also be partly due to a certain resistance on the part of mothers of social classes IV and V to delivery in hospital with the resultant refusal to accept advice on the need for hospital booking. The survey suggests that hospital booking should be related to social class rather than to poor home circumstances, and it considers that a social class high risk booking should be regarded as a medical hospital indication and that "poor home circumstances" should be regarded as an indication for booking at a general practitioner unit in preference to a home delivery.

The exact significance of several factors is difficult to interpret, notably that patients delivered in private nursing homes show no real variation in mortality ratio regardless of their social class. This is, of course, a small group comprising only $2 \cdot 3 \%$ of the total patients. Patients who are unbooked, regardless of whether they are confined in hospital or at home, have a remarkably high mortality ratio (500) and it seems obvious that unbooked patients should not be delivered at home. The mortality ratio of unbooked patients follows a trend exactly opposite to the rest of the population. The mortality ratio is highest in social class I (597) and lowest in social class V. It seems, therefore, that there is another factor operating which is exactly parallel to social class and which therefore weights the overall mortality of the lower social class. This factor does not seem to have been elucidated in the Perinatal Mortality Survey.

An analysis of the movement of patients after their initial booking shows that this is always towards hospital and in fact $40 \cdot 9 \%$ of patients are booked for hospital confinement and yet $49 \cdot 1 \%$ are ultimately delivered there. There are marked regional variations

in the percentage of patients delivered in hospital, home and general practitioner unit beds. London and the South-East region has by far the highest percentage of hospital deliveries (64% approximately) which is almost double that of the Southern region (where approximately 36% of patients are delivered in hospital), and yet the mortality ratio of the two regions is almost identical (Table 19). This may be the result of very efficient and careful selectivity in the Southern region.

Where there are a greater number of hospital beds available there are proportionately fewer patients moved from both home and general practitioner units into the hospital with a consequent reduction in this particularly high risk group. All these analyses, however, do not provide the answer as to why some regions have a higher mortality than others. In most of the regions with a high overall mortality ratio it is noticeable that the mortality ratio in all social classes is higher than those of the regions in which there is a lower total mortality ratio. The one exception to this is Wales, which has a particularly high mortality ratio for social class III only. In fact, the overall mortality within all the regions is directly related to their ability to deal efficiently with the largest social class, that is social class III.

Antenatal Care

Some mothers (0·6%) receive no antenatal care and they account for 3·2% of the deaths. This represents a mortality ratio of 502, i.e. five times the overall national figure. The mortality ratio then falls gradually with the number of antenatal visits, and it is lowest within the group who pay between 15 to 24 visits (where the ratio is 58). Patients who are seen more than 24 times have a gradually increasing mortality ratio, probably as a result of illness which necessitated their being seen more frequently.

Less than half of all mothers (48·8%) attend for their first antenatal visit before the 16th week of pregnancy. This is surely a serious reflection upon the modern standards of education. Perhaps a publicity campaign designed to encourage women to attend for their first antenatal visit earlier would be one of the most simple and yet most efficient ways of attacking the present perinatal mortality rate (Table 29). Fifty-six per cent of nulliparæ attend for the first time before the 16th week, but only 3·9% of mothers attend before the 8th week. It is indeed scandalous that one-third of all patients having their fifth or subsequent child receive no antenatal care

Table 27

DISTRIBUTION OF THE POPULATION BY PARITY AND THE DURATION
OF THEIR PREGNANCY AT THEIR FIRST PRENATAL VISIT

PARITY	WEEK OF FIRST VISIT	NO PRE-NATAL VISITS	1-7	8-15	16-23	24-31	32-35	36 or later	NOT KNOWN	TOTAL =100%
PARA.0	No	46	294	3250	1799	583	99	44	169	6284
	%	0.7	4.7	51.7	28.6	9.3	1.6	0.7	2.7	
PARA. 1	No	13	214	2473	1691	582	83	39	120	5215
	%	0.3	4.1	47.4	32.4	11.2	1.6	0.7	2.3	
PARA. 2	No	12	74	1067	967	378	66	17	70	2651
	%	0.5	2.8	40.2	36.5	14.3	2.5	0.6	2.6	
PARA. 3	No	8	41	438	512	233	44	16	34	1326
	%	0.6	3.1	33.0	38.6	17.6	3.3	1.2	2.6	
PARA. 4+	No	21	39	405	491	370	100	35	55	1516
	%	1.4	2.6	26.7	32.4	24.4	6.6	2.3	3.6	
TOTAL	No	100	662	7634*	5460	2146	392	152*	448	16994*
	%	0.6	3.9	44.9	32.1	12.6	2.3	0.9	2.6	

* These totals include
cases of Parity not known.

until after the 24th week of pregnancy, and one wonders if herein lies the secret of the high mortality in this group. It is also sad to reflect that a further one-third of this group attend for the first time between the 16th to the 23rd week. It is unfortunate that the survey has not undertaken any cross reference between the date of first attendance and the social class, or the date of first attendance and the mortality ratio. Perhaps herein lies the reason for the high mortality rate in social classes IV and V.

The modal number of antenatal visits in the whole series was 10 to 14. This applied in the high risk hospital group, where the mortality ratio was 101, which closely approximates to the national average of 100. Where the hospital shared the antenatal care the mortality ratio rose fractionally to 107. Where the antenatal care was conducted by general practitioners only, the modal number of visits was 5 to 9 and the mortality ratio rose to 126. In both of these groups the higher mortality has occurred in what should have been a comparatively low risk group and stresses the importance of antenatal care and of the frequency of antenatal visits. It is also notable that those patients seen by the general practitioner alone contain a comparatively high proportion of patients from social

classes group I and II which ought, therefore, to have a low mortality ratio. A large proportion of those patients who had no antenatal care fell into social classes IV and V.

Hæmoglobin Levels

One-third of all pregnant women in the Perinatal Mortality Survey did not have a hæmoglobin level estimated at any stage during their pregnancy (Table 28) and $4 \cdot 7^{\circ}$ of those patients attending hospital for their complete antenatal care did not have a hæmoglobin estimation during their pregnancy. This figure rose to $18 \cdot 4^{\circ}$ for those in which the hospital shared the antenatal care and $35 \cdot 2^{\circ}$ of those attending local health authority clinics did not have their blood tested. Those attending the general practitioner and midwife, and the midwife only, failed to have their hæmoglobin estimated

Table 28

THE PERCENTAGE OF POPULATION WITH NO HÆMOGLOBIN TEST
BY GRADE OF PRENATAL CARE

Grade of Prenatal Care	% Mothers no result
Hospital only	4.7
Hospital in part	18.4
L.H.A. clinic throughout or in part	35.2
G.P. only	60.0
G.P. and Midwife	67.9
Midwife only	77.5
None	65.3
No information	33.8

in $67 \cdot 9^{\circ}$ and $77 \cdot 5^{\circ}$ of cases respectively. As the estimation of the hæmoglobin is one of the basic and essential investigations during pregnancy these results are surprising. A hæmoglobin estimation should be performed at least twice in each pregnancy and there seems little excuse why such a simple investigation should not be undertaken.

The exact figures of hæmoglobin levels given in the survey are not very informative, and it does not state at what stage of pregnancy the hæmoglobin estimations were performed. Speaking only in the broadest sense, however, there does appear to be a higher incidence of anæmia in those areas having a higher mortality ratio. It is noted that those patients who have a hæmoglobin level of below 60° have a mortality ratio twice that of the national average.

Blood Pressure

Nearly all patients (98·4%) attending hospital for antenatal care have their blood pressure taken at each visit but approximately 20% of those attending elsewhere for their antenatal care did not. The worst figure (25·4%) is for those patients attending both the general practitioner and the midwife, where possibly each of the two supervisors considered that the other was undertaking a blood pressure estimation. This error can be eliminated by using an antenatal co-operation card which the mother keeps and in which all findings are documented at each visit.

These figures leave considerable room for improvement.

The mortality ratio for patients who are normotensive is 76, but patients with essential hypertension have a mortality ratio of 104, whilst the mortality ratio for pure toxæmia of pregnancy is 108, and unclassified toxæmia 135. The more severe the pre-eclamptic toxæmia the higher the mortality ratio, and the presence of protein in a catheter specimen of urine is a particularly dangerous sign, because in such cases the mortality ratio rises to three times the national average. 34·2% of all patients having their first baby have at least one diastolic blood pressure recording of 90 mm. of mercury or more. Between 22% and 24% of all subsequent pregnancies have one diastolic blood pressure recording of 90 mm. of mercury or more. These patients have a mortality ratio of 124. Using this strict level as diagnostic the overall incidence of hypertension of pregnancy is 27·5%. Toxæmia is a major cause of transfer of cases either in late pregnancy or in labour. The incidence of toxæmia is 40·1% in patients transferred from home to hospital and 47·7% in patients transferred from general practitioner units to hospital. There is a strong suggestion that poor antenatal care is responsible for allowing toxæmia to develop unobserved, since incomplete data on toxæmia occurs in 17·8% of home to hospital transfers and 22·7% in general practitioner unit to hospital transfers. At every week of gestation after the 32nd week the mortality is always greater than that in normotensive patients.

Rhesus Factor

Seventeen and a half per cent of patients studied in the survey were rhesus negative but 5·5% of all patients did not have their rhesus type estimated during pregnancy. This refers to rhesus type only and not to complete blood grouping. In only 0·7% of those

patients attending hospital for their antenatal care was the rhesus type not known, but in 12% of those attending general practitioners and 13% of those attending general practitioners and midwives was the rhesus type not known (Table 29). It may well be that a number of general practitioners consider it unnecessary to perform the rhesus type in a primigravid patient, but this is wrong for even a primigravida can have antibodies and estimation of the rhesus factor is an essential investigation of pregnancy.

Table 29

THE PERCENTAGE OF THE POPULATION FAILING TO HAVE
CERTAIN ROUTINE PRENATAL TESTS

Grade of Prenatal Care	No Haemoglobin Test	Blood Pressure: Not always tested	Rh. type: No Test and No Record
Hospital only	4·7	1·6	0·7
Hospital in part	18·4	17·2	1·7
L.H.A. clinic throughout or in part .	35·2	18·6	4·8
G.P. only	60·0	17·8	12·0
G.P. and Midwife . . .	67·9	25·4	13·0
All cases	33·3	15·9	5·5

In only 3·8% of patients having their first baby was the rhesus factor not determined, and the percentage rose until, in patients having their fifth child, 11·4% had not been tested.

The mortality ratio amongst rhesus negative women having their first baby is lower than the average and also lower than for rhesus positive women. This may be due to their better antenatal care and hospitalization. As parity increases, however, the mortality ratio amongst rhesus negative women rises. A woman who is rhesus negative and who is having her fifth baby has a 75% higher risk of losing her baby than if she were rhesus positive. Approximately one-third of all the deaths occurring in rhesus negative patients having their fifth and subsequent child are due to rhesus iso-immunization, yet the rhesus type is not known in 11·4% of all patients in this group.

Bleeding in Pregnancy

Six per cent of the patients studied in the survey bled from the genital tract at some stage during their pregnancy. It should be remembered that these were all patients who had reached the 28th week of gestation and it does not include any patient who miscarried before that time. Vaginal bleeding before 28 weeks only

Table 30

THE INCIDENCE OF BLEEDING IN PREGNANCY IN THE POPULATION WITH
THE ASSOCIATED DEATHS AND THE SURVEY MORTALITY RATIO (M)

Type of Bleeding	Population		Deaths		Survey Mortality Ratio (M.)
	No.	%	No.	%	
Vaginal bleeding pre 28 weeks only .	498	2·9	495	7·0	237
All antepartum haemorrhages . .	527	3·1	1256	17·6	568
Antepartum haemorrhages with vaginal bleeding pre 28 weeks only. . .	90	0·5	202	2·8	534
No bleeding	15960	93·9	5366	75·4	80

occurred in 2·9%, whilst 3·1% of patients suffered from antepartum hæmorrhage with or without previous bleeding before the 28th week (Table 30).

Women suffering from vaginal bleeding before the 28th week of pregnancy (2·9%) account for 7% of the perinatal deaths with an overall mortality ratio of 237, which is three times the mortality ratio (80) for the remainder who did not suffer from bleeding of any type during pregnancy. Bleeding before the 28th week of pregnancy increases very slightly the risk of premature labour before the 31st week of pregnancy. The mortality ratio, however, of patients who have bled before the 28th week is considerably increased at all stages of gestation, especially for those infants born prematurely, and one rather astonishing finding of the survey is that women who have bled prior to 28 weeks and who deliver before the 38th week of pregnancy have a mortality ratio 26 times greater than those who deliver after the 38th week of pregnancy.

It seems as though those patients who deliver after the 38th week fall into a relatively low risk group and those who deliver before the 38th week fall into an extremely high risk group, and there appears to be no way of differentiating between these two groups at an earlier stage of their pregnancy. Therefore, any patient who bleeds in pregnancy before the 28th week falls automatically into an extremely high risk group and should be admitted to hospital for confinement.

The remaining 3·1% of patients who suffer from antepartum hæmorrhage (with or without bleeding before the 28th week) showed a mortality ratio of 568, which is eight times greater than those who do not suffer from any form of hæmorrhage (Table 30). This group

accounted for $17 \cdot 6 \%$ of the total perinatal mortality. These patients can be further subdivided into those who suffered from accidental antepartum hæmorrhage, in whom the mortality ratio was 23 times that of those who had no bleeding; those suffering from plancenta prævia, in whom the mortality ratio was $4\frac{1}{2}$ times that of those who had no bleeding; and those suffering from unspecified antepartum hæmorrhage, in whom the mortality ratio was 5 times that of those who had no bleeding. These figures only serve to underline the well-known hazard presented by accidental antepartum hæmorrhage.

An analysis of patients suffering from antepartum hæmorrhage compared with those who suffer from pre-eclamptic toxæmia or essential hypertension shows that at least one-third of those patients who suffer from accidental antepartum hæmorrhage have no association with either hypertension or pre-eclamptic toxæmia.

A number of patients included under the heading of bleeding before the 28th week of pregnancy have in fact threatened to abort in early pregnancy and later have gone into premature labour before the 28th week, being delivered of a pre-viable but nevertheless live fœtus which automatically has a very high mortality rate.

It is well known that babies associated with a toxæmic pregnancy have a higher perinatal mortality than those babies from a non-toxæmic pregnancy. The lowest mortality ratio in pre-eclamptic toxæmia occurs from the 39th to the 41st week, but this figure is probably heavily weighted by the inclusion of many mild toxæmias. The mortality ratio of a toxæmic patient after 41 weeks gestation is approximately twice that of those in the non-toxæmic group. Only $2 \cdot 5 \%$ of births occur at 43 weeks with an overall mortality ratio approximately double that at term, but $0 \cdot 8 \%$ of births occur at the 44th week or later and the mortality associated with such prolonged pregnancy is three times that at term.

It can be estimated from the statistics of the Registrar-General for England and Wales that approximately 86,900 women had pregnancies exceeding 42 weeks in 1958. If the survey figures are correct, that there is an increase of 72% in the mortality after the 42nd week, then this means that approximately 2,000 children died in 1958 in whom death could be directly attributed to, or associated with, postmaturity. These figures do not take into account those patients who were induced on account of postmaturity, so the intrinsic risk of this condition is therefore probably greater than these figures would suggest. It is appreciated that there is consider-able argument regarding the advantages of induction of patients

purely on the grounds of postmaturity, but nevertheless the figures in the survey do indicate that postmaturity *per se* presents a considerable hazard. Similarly, the survey results confirm the increased hazard to the fœtus of prolonged pregnancy in the presence of even mild pre-eclampsia.

Women between the ages of 20 to 29 fall into the most favourable age group for child bearing, with the lowest mortality ratio of 32 being present in women of 24 years of age delivered at 40 to 41 weeks of gestation. There is a progressive tendency to eliminate postmaturity in all women over the age of 30. At 40 to 41 weeks maturity women between the ages of 35 to 39 have twice the mortality ratio of women between the ages of 20 to 29. Patients over 40 years in whom pregnancy has lasted for 42 weeks or longer, have a mortality ratio two and a half times greater than that present in those women between the ages of 20 to 24. The risk of postmaturity extends through all age groups regardless of their parity, although as parity increases above gravida 5 so does the danger of postmaturity.

Maturity

The high death rate amongst immature babies is well known and need not be further discussed here. In 6.7% of the population the infant birthweight was 2,500 g. or less and these infants suffered from an overall mortality ratio of 795, which is approximately eight times that of the national average.

The mortality rate increases steadily when maternal age exceeds 30 in all the weight subdivisions over 2,500 g., so that both maternal age and birthweight appear to exert a direct influence upon, or to be directly related to, the mortality ratio.

In women of social class I only 3.6% of babies were premature, whereas in women of social class V 7.2% of babies were premature and women with no husbands had a prematurity rate of 10.8%.

Labour and Delivery

A total of 2.7% of patients were delivered by Cæsarean section, which carried a mortality ratio of 225, doubtless reflecting the severity of the conditions for which Cæsarean section was performed, but the survey underlines and emphasizes the danger of performing Cæsarean section with undiagnosed immaturity with the resulting production of a small baby who may succumb in the neonatal period.

Consultants perform the delivery in 2·8% of women and directly supervise the delivery at a total of 14·4% of all confinements, which is not even one-third of those who are delivered in hospitals. General practitioners conduct the delivery in 4·4% and are present at an additional 7·3%. This figure is not very high when it is considered that 48·5% of patients are delivered either in general practitioner units or at home, where the majority are under the direct responsibility of the general practitioner.

Trained midwives actually deliver 52·6% of all mothers and are the responsible person present at 70·4% of all births because they are entrusted with the supervision of both medical students and pupil midwives.

Who delivers whom? In hospital-booked cases a midwife is the senior person present in 70·5%. In home-booked cases the midwife is the senior person present in 85·9% of cases. In general practitioner units the midwife is the senior person present in 69·3% of cases. Whilst in no way wishing to underrate the ability or the value of the midwife in her care of the maternity patient, it seems reasonable to suggest that a higher proportion of mothers should be medically supervised.

Duration of Labour

The majority of primigravidæ deliver after a first stage which lasts between 6 to 24 hours. In fact, 31% have a first stage of between 6 to 12 hours and 34% have a first stage which lasts between 12 to 24 hours. A particularly rapid first stage carries a high perinatal mortality and this may be associated with prematurity, but strangely enough the 13% who delivered after a first stage of between 24 to 48 hours had a mortality ratio of 95, which is lower than average. The mortality ratio climbed to 156 after 48 hours, but it does not appear to make any difference how long labour continued after the 48 hour period as the mortality ratio does not rise any further. Sixty-five per cent of multiparous patients were delivered within 12 hours and, as might be expected, the mortality ratio climbed rapidly in those patients who laboured for more than 24 hours.

Thirteen per cent of patients delivered at home, and 15% of patients delivered in general practitioner units, have a first stage which lasts for more than 24 hours. It would seem reasonable to suggest that any patient who is booked outside hospital and whose labour lasts for 24 hours should be transferred for consultant care for the remainder of the labour.

The survey comes to the following conclusions regarding the duration of labour:

1. More research is needed into the risks of short labour (although these may be associated with immaturity).
2. Primigravidæ and multigravidæ with a first stage of 24 hours or more require immediate transfer to hospital.
3. Primigravidæ and multigravidæ with second stages of 120 or 60 minutes respectively require immediate delivery. (This is sound obstetric practice, and the figures of the survey do indicate a rise of mortality in those patients in whom the second stage is unduly prolonged.)

Analgesia in Labour

The survey classifies the use in regions of various analgesic agents and 34% of patients received no analgesic drug during the 12 hours prior to delivery.

Inhalation Analgesia

In 1958 when the survey was undertaken gas and oxygen analgesia was little used, in fact only 0·3% of labouring women received it, whereas 55% of the mothers received gas and air analgesia. Two per cent received trilene in addition. It is now accepted that the reduction of oxygen intake consequent upon the inhalation of gas and air is not in the best interests of the fœtus and that this type of inhalation anæsthesia should be discontinued and replaced by gas and oxygen. 22·6% of the mothers received trilene inhalation.

The Eastern and Southern Counties, which have the lowest perinatal mortality rate, also have the highest utilization of volatile analgesics.

Forceps Delivery

The incidence of forceps delivery in the survey was only 4·7%, which included an overall forceps incidence in primigravidæ of 10·5%.

It is interesting to note that in 62% of forceps deliveries there was no evidence of fœtal distress and the operation was done for delay in the second stage, or for maternal reasons such as toxæmia or heart disease. In this group the overall mortality ratio was 97, clearly indicating that the mortality ratio of forceps deliveries is related to the indication for the operation and not to the operation itself.

Ten and a half per cent of all primiparæ are delivered by forceps (as compared with $4\cdot7\%$ of the patients as a whole), the highest incidence of $11\cdot9\%$ occurring in hospital booked and delivered cases whilst the incidence is $8\cdot4\%$ in general practitioner units and only $3\cdot7\%$ in patients booked and delivered at home. It is rather disturbing to find that the mortality ratio of forceps deliveries in general practitioner units is 128 (as compared with 93 at home and 82 in hospital) and this is despite the fact that the difficult cases are transferred to hospital and the mortality ratio of forceps deliveries in patients transferred from general practitioner units to hospital is 214, whereas as that occurring in those transferred from home to hospital is 150. A more careful selection is clearly indicated.

Consultants or Registrars perform $43\cdot6\%$ of forceps deliveries, with a mortality ratio of 156, and this group probably includes the majority of the difficult forceps deliveries. House Officers deliver $36\cdot1\%$ of forceps deliveries with a mortality ratio of 78. This group undoubtedly includes those patients of the lowest intrinsic risk and it clearly demonstrates that there is no intrinsic risk in the correct application of the forceps at the correct time. The risk more likely lies in the indication rather than the actual application of the instrument. This group should be comparable with the deliveries performed by general practitioners, who undertake $19\cdot4\%$ of forceps deliveries but have a mortality ratio of 126. Whilst accepting that many general practitioners may be working in the home under unsuitable circumstances these figures clearly indicate that there is inadequate selection of such patients and that the majority, if not all of them, should in fact be delivered in a consultant unit.

General anæsthesia was used in hospital for $51\cdot7\%$ of forceps deliveries and pudendal block or local infiltration was used in $46\cdot8\%$. Bearing in mind that these figures apply to 1958, it is probable that the incidence of local anæsthesia or pudendal nerve block has increased at the expense of general anæsthesia. In general practitioner units general anæsthesia was given for $85\cdot4\%$ of forceps deliveries and pudendal nerve block in only $10\cdot3\%$, whereas in home delivery general anæsthesia was given in $84\cdot1\%$ and $9\cdot5\%$ had a pudendal nerve block or local anæsthetic. In view of the dangers of general anæsthesia in obstetrics it is highly desirable that the incidence or percentage or pudendal nerve block and local anæsthesia should be increased in all three localities of delivery, but more especially in the general practitioner units and the home.

Breech Delivery

The mortality ratio in the survey of breech delivery is 702, which is seven times the overall baby risk and it is interesting to note that the mortality ratio for breech presentations delivered by Cæsarean section is 246 and that 14·8 % of all breech presentations are delivered by Cæsarean section.

The exact figures on breech delivery are difficult to interpret because of the inclusion of many cases of dead babies, prematurity and congenital abnormalities.

Thirty-five per cent of all vaginal breech deliveries are performed by midwives, pupil midwives or medical students who may or may not be supervised, with a mortality ratio of over 1,000. Even allowing for stillbirths and prematurity this is an extraordinarily high mortality ratio and one cannot help but conclude that it is absolutely essential for all breech deliveries to be conducted or supervised by a senior medical officer. Occasionally errors of diagnosis or prematurity may force the general practitioner or the midwife to deliver a breech at home or in a general practitioner unit, but this should amount to only a small percentage of the total number of vaginal breech deliveries.

The survey again underlines the dangers of prematurity in association with breech delivery, and it illustrates that the lowest mortality for breech deliveries occurs in babies between the weight of 3,000 g and 3,500 g. Above this weight the mortality ratio climbs rapidly. There is obviously an increasing place for Cæsarean section in the delivery of the large infant. Perhaps the trial of breech labour which depends upon the spontaneous descent of the breech through the pelvis would indicate more clearly the relative size of the breech and the pelvis, and in instances of delay, or poor descent, Cæsarean section should be performed even after the second stage of labour has commenced.

Twenty-seven per cent of breech deliveries are conducted either in the home or in the general practitioner unit. 48·3 % of patients who had a breech delivery in hospital received no anæsthetic, which is an unforgivable condemnation of either the obstetric or the anæsthetic services provided. General anæsthesia was given for 20 % of breech deliveries and local or pudendal nerve block was used for 30 %. As the survey correctly points out there is some controversy concerning the advisability of general anæsthesia versus regional anæsthesia in breech delivery, but all are agreed that a general

anæsthetic should be instantly available and that a skilled anæsthetist must always be present at a breech delivery in case his services are required unless conduction anæsthesia (epidural or caudal) is being used. In the general practitioner unit 70% of patients in breech labour had no anæsthetic, and in domicillary breech deliveries 88·3% of mothers failed to receive any form of anæsthesia. These figures emphasize that in both general practitioner units and in the home the services of a skilled anæsthetist are not always available.

As stated above, there is no excuse for the elective delivery in the home of the fœtus presenting by the breech, nor is there any excuse for the elective delivery of breech babies in the general practitioner unit unless all the required facilities are readily available.

Induction of Labour

Amniotomy was performed as a method of induction of labour in 7·6% of mothers (that is in over half of the patients induced). In 30·7% low rupture was performed and in 43·1% high rupture was performed, whereas in 26·2% both high and low rupture were used, or the information regarding the type of rupture was incomplete. There was no difference in the incidence of Cæsarean section following either high or low rupture (5·2% and 4·8% respectively). Eighty-seven per cent of patients who were induced by low rupture of the membranes were delivered within 48 hours, as compared with only 71% of those patients who were induced by high rupture of the membranes. The incidence of intra-uterine pneumonia in deaths after high rupture was 11·2%, as compared with only 6% after low rupture. This is one of the many factors which indicate the advantage of low rupture over high rupture, which should be abandoned except in very exceptional circumstances.

Oil, bath and enema with or without membranes sweep, and with or without oxytocic agents was used in 4·8% of women. As a technique for the induction of labour this is not to be encouraged. A large dose of castor oil, a hot bath and an enema is quite an efficient combination in contributing to the dehydration of a patient and may easily be a factor in disturbing the electrolyte balance; especially when such procedure is followed by many hours of starvation during the stresses and strains of labour which may be prolonged, and which may culminate in the administration of a general anæsthetic and be associated with the trauma and blood loss of delivery.

Summary

This chapter has dealt mainly with a number of the ætiological factors revealed by the Perinatal Survey as influencing the perinatal death rate in Britain. The published survey also contains a detailed analysis of the exact causes of death occurring in the selected material in March 1958.

It is appreciated that in this chapter problems of perinatal mortality have not been considered in detail. If some of the fundamental principles that have been discussed could be satisfactorily applied, if some of the omissions could be corrected, if greater care could be given to the pregnant woman in some of the ways indicated, and if she herself could be encouraged to co-operate more fully, then the rewards would be great. The correction of these obvious defects in the maternity service is of fundamental importance. Many of them are similar to those revealed by the Enquiry into Maternal Mortality (Chapter 1).

ANÆMIA IN PREGNANCY AND THE PUERPERIUM

by

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Anæmia may be defined as a diminution below normal in the total circulating hæmoglobin mass. Estimation of this is not a simple matter. We ordinarily accept such estimations as the hæmoglobin *concentration*, red cell concentration and packed cell volume as indicating the presence or absence of anæmia and, in the former case, its degree. It must, however, be realized that these rarely assess the anæmic state accurately. For example, a severe rapid loss of blood will produce anæmia, that is, immediate deficiency in the total circulating hæmoglobin mass, but the ratio of plasma to cells and the composition of the red cells, and therefore the hæmoglobin concentration, red cell concentration and packed cell volume will not be affected immediately. In chronic nutritional anæmia the hæmoglobin concentration underestimates the severity of the anæmia, for in this condition there is a reduction in red cell volume while the plasma volume remains constant.

The opposite occurs in pregnancy. The total hæmoglobin mass may not be diminished (it may in fact be increased), but a disproportionate increase in plasma volume causes a reduction in hæmoglobin concentration, red cell concentration and packed cell volume. As will be seen, the changes in total hæmoglobin mass and in plasma volume vary so widely from patient to patient that it is impossible to give a reasonable definition of the normal range of hæmoglobin concentration or total circulating hæmoglobin mass in pregnancy.

Blood Volume in Pregnancy

Among the earliest workers to observe the changes in blood volume which occur in pregnancy were Dieckmann and Wegner (1934). They showed that the plasma volume begins to increase during the first trimester and reaches, on average, a value at term

about 25% above the normal non-pregnant value. The figure does not return completely to normal by the 8th week of the puerperium. They also observed an increase of 13% in the total circulating hæmoglobin mass and of 20% in the red cell volume. These increases being less than the increase in plasma volume, there is a fall in hæmoglobin concentration and red cell concentration although there is not a true anæmia. They estimated that at about the 30th week of pregnancy, when the hæmodilution is most marked, the average fall in hæmoglobin concentration is 2·2 g./100 ml. (15%) and that true anæmia is not necessarily present *in the later stages of pregnancy* until the hæmoglobin concentration has fallen below 10 g./100 ml. (68·5%).

This level of 10 g./100 ml. is the one which has been most widely used for estimating the incidence of anæmia in pregnancy, even among women first attending the antenatal clinic when, in the majority of cases, little or no hæmodilution has yet occurred. It must be realized at once that neither this not almost any other figure can be used to determine whether a given patient is anæmic or not, except in the earliest stages of pregnancy when the figure of 10 g./100 ml. is much too low. In Dieckmann and Wegner's and all subsequent work it has been shown that there is considerable individual variation in these volume changes during the course of pregnancy and that a proportion of patients do not appear to show any very significant changes at all. In fact, as will be seen, adequate treatment will maintain the hæmoglobin concentration throughout pregnancy at levels significantly higher than 10 g./100 ml. in the great majority of cases.

As more accurate techniques were developed the findings of Dieckmann and Wegner were verified and modified. It was shown that the increases were greater than they had reported and that the maximum plasma volume increase occurred about a month before term, being followed by a slight fall during the last month of pregnancy. During labour and the immediate postpartum period the blood volume fluctuates widely (Brown *et al.*, 1947; Duhring, 1962) because of the uterine contractions and the rapidly changing functional demands. The effects in pregnant cardiac cases may be grave and many develop congestive cardiac failure in the first postpartum day. Seventy-five per cent of maternal cardiac deaths occur in the immediate postpartum period.

Of particular interest, in view of the increasing frequency with which it is suggested that there is no such thing as "physiological anæmia" of pregnancy (a state of hæmodilution sufficiently great

to cause a significant fall in hæmoglobin concentration) and that it can be prevented by iron therapy, is the fact that although the patients observed by Berlin *et al.* (1953) were given iron throughout pregnancy and those of Caton *et al.* (1951) were not, very similar results were obtained by both groups of workers. Berlin *et al.* concluded therefore that iron does not prevent the physiological anæmia of pregnancy. They also showed that after parturition there is a fall in red cell volume to below the normal non-pregnant value. Verel *et al.* (1956) verified this and demonstrated that it could not be accounted for entirely by hæmorrhage at delivery, but that there must be then or shortly afterwards a rapid removal of red cells from the circulation.

These changes in intravascular fluid and cell volumes are accompanied by large increases in the extravascular fluid volume (Caton *et al.*, 1951). This extra fluid is rapidly lost in the first week postpartum.

An important contribution was made by Lund and Sisson (1958). They classified women according to their blood volumes into three groups, hypovolæmic, isovolæmic and hypervolæmic, and showed that they tend to remain within their own group during pregnancy. All three groups show an increase in plasma volume during pregnancy, this being greatest in the hypervolæmic group and least in the hypovolæmic. The hypovolæmic woman, with a plasma volume of 40 ml./kg. body weight before pregnancy, might show a maximum plasma volume during pregnancy of 55 ml/kg., while the hypervolæmic woman might have a plasma volume as great as this in the non-pregnant state. They stressed the very wide variation in blood volume figures from patient to patient, pointing out that two of their patients of similar body weights, hæmoglobin concentrations and packed cell volumes had total blood volumes and total hæmoglobin masses differing from each other by 100%.

To summarize then, from very early in pregnancy there is a continuous increase in plasma and extracellular fluid volumes, the former showing a slight recession during the last few weeks of pregnancy, while the latter continues to increase until parturition. The red cell volume may fall during the first two months of pregnancy but rises thereafter, to a lesser degree than the plasma volume, until the last month when it begins to recede. During and immediately after parturition wide fluctuations in blood volume occur. Thereafter the red cell volume falls rapidly to slightly subnormal values and recovers slowly, while the plasma and extravascular fluid volumes fall more slowly. Not all women show these changes equally. Those

with low initial plasma volumes tend to show them to a minor degree, while those with high initial plasma volumes tend to show them to a marked degree.

Certain work has led to claims that the concept of physiological anæmia of pregnancy due to disproportionate increase of plasma over red cells is false. Such claims are based almost entirely on observations of the hæmoglobin concentrations during pregnancy, which can be shown to rise in many cases if adequate iron is given. It must, however, be apparent that if a patient is anæmic at the commencement of pregnancy and is given adequate iron therapy, the total hæmoglobin mass may increase to such a degree as to mask the effect of hæmodilution on the hæmoglobin concentration. No investigations of the blood volume changes have failed to demonstrate this hæmodilution by relative plasma increase in the absence of significant initial anæmia.

The evidence seems incontrovertible. The studies quoted, and many others, are in general agreement and, as has been pointed out, the volume changes are essentially similar whether the subjects are receiving iron or not. Lund and Sisson (1958) compared the red cell volumes, hæmoglobin masses, packed cell volumes and hæmoglobin concentrations of a group of 17 non-pregnant women at mid-menstrual cycle, with no clinical or laboratory evidence of anæmia, with those of 8 women in uncomplicated pregnancy on an adequate diet. Their results are shown in Table 31. As can be seen, the pregnant women showed the lower packed cell volumes and hæmoglobin concentrations, although their total red cell and hæmoglobin masses were very much the greater. By no stretch of the imagination

Table 31

COMPARISON OF HAEMOGLOBIN AND RED CELL VOLUME VALUES IN PREGNANT AND NON-PREGNANT WOMEN

	Total (body)		Venous	
	Red cell vol. ml/kg.	Haemoglobin mass g/kg.	Haematocrit per cent	Haemoglobin g. per 100 ml.
Non-pregnant				
Highest	34	11·8	45	14·0
Lowest	24	8·8	35	11·5
Mean	28	10·0	40	12·5
Pregnant				
Highest	39·8	15·1	38·5	12·9
Lowest	31·0	11·0	29·0	8·8
Mean	33·9	12·3	33·2	10·9

can their rather low hæmoglobin concentrations be called "pathological".

Nevertheless, the evidence against the concept of physiological anæmia of pregnancy must be examined. Benstead and Theobald (1952) found that oral iron maintains the hæmoglobin concentration in pregnancy and deduced that there is no such thing as physiological anæmia in that it can be prevented by iron therapy. However, the majority of their patients were anæmic when iron therapy commenced (60% had hæmoglobin concentrations below 12 g./100 ml.). The same criticism applies to the work of Davis and Jennison (1954), whose observations are further complicated by the fact that they compared the hæmoglobin concentrations at 30–34 weeks when hæmodilution is approaching its maximum and the hæmoglobin concentration its minimum, with those at term when some recession in hæmodilution and natural rise in hæmoglobin concentration is to be expected, and concluded that iron prevents the physiological anæmia of pregnancy. Fisher and Biggs (1955) gave oral iron to 104 pregnant women and found that 92 responded and 12 did not, the criterion of response being a hæmoglobin of 12·6 g./100 ml. (86%) at 38 weeks. The non-responders showed a general downward trend in hæmoglobin concentration with a sharp postpartum rise to responder levels. In addition, a further 11 cases had initial hæmoglobins of 14·6 g./100 ml. (100%) or more. These showed a steady fall in hæmoglobin concentration throughout pregnancy. In similar studies by Edgar and Rice (1956) the incidence of non-responders was 22·4%. They suggest that these patients did not take their iron or failed to absorb it, but offer no evidence of this. In their series the hæmoglobin levels of their responders even, tended to fall slightly until the 32nd to 36th week and thereafter to rise. It should be noted also that the final hæmoglobin concentrations achieved during these studies were not, on average, as high as those obtained with iron therapy in non-pregnant women by Widdowson and McCance (1936) and Yudkin (1944) whose work will be discussed later.

Recent work has verified that the conclusion that the non-responders failed to take or to absorb their iron is unacceptable. Thus Giles and Burton (1960) found that about 8% of their patients showed no response to iron during pregnancy. However, they showed a rise of about 0·75–3 g./100 ml. in hæmoglobin levels after delivery, whereas the mean postpartum rise for the whole of their series was 0·22 g./100 ml. They concluded that failure to respond to iron was apparent rather than real, and was due to greater

hydræmia in the non-responder group. The work of Lawrence (1962) showed that this conclusion was correct. He compared a series of patients with hæmoglobins below 12·7 g./100 ml. (86%) *late in pregnancy* with one with hæmoglobin concentrations above that figure, and found that the plasma volumes were much greater in the former group. After delivery the hæmoglobin concentrations in both groups settled at about 13·6 g./100 ml. (93–94%).

The correct conclusion from observations on the effect of iron therapy on the hæmoglobin concentration appears therefore to be that, in 9 out of 10 women iron will maintain the hæmoglobin concentration at 12·6 g./100 ml. or more, or raise it to such levels if there is significant initial anæmia. In the remainder there will be no such apparent response to iron. In these cases, however, the response will have been masked by their greater plasma volume increase, but will have taken place nevertheless. It cannot be said therefore that, in late pregnancy, a woman with a hæmoglobin concentration of 12·6 g./100 ml., or even, as can be seen from Table 31, of 8·8 g./100 ml. is necessarily anæmic in the true sense. The concept of physiological anæmia of pregnancy must be accepted.

The causes of these changes are not yet clearly understood. It is probably true to say that the increase in red cell volume and a proportionate fraction of the increase in plasma volume is explained by the growth of maternal tissues and the nature of the placental circulation which resembles a large arterio-venous fistula, and that this increase is obtained by an increase in red cell production under the influence of an increase in erythropoietin. The increase in red cell volume is not dependent on iron therapy and occurs in women not given iron (Lowenstein *et al.*, 1960; Paintin, 1962). Nevertheless, iron deficiency limits this increase and may even cause a fall (Lawrence, 1962; Lowenstein *et al.*, 1960; Paintin, 1962). It also has a limiting effect on the plasma volume increase (Lawrence, 1962).

The remaining increases in plasma and extracellular fluid volumes are not as easily explained and commence early in pregnancy before the placenta is formed. It seems likely that they are related to the alterations which occur in hormone balance, but the evidence is far from complete. Furth and Sobel (1947) have observed blood volume increases in mice with œstrogenic granulosa tumours, and there are considerable increases in œstrogens during pregnancy. Hytten and Klopper (1963) demonstrated that the ability to excrete a water load, increased earlier in pregnancy, decreases steadily after the 30th week, when the plasma and extracellular fluid volumes

increase most rapidly. They suggest that the decreasing ability to excrete a water load is due to the antidiuretic effect of the increasing concentrations of œstrogens and posterior pituitary hormones. In this connection Kaplan (1961) has made an important observation. A pregnant woman had had a hypophysectomy. Her diabetes insipidus was controlled with pitressin. Her pitressin requirements fell as pregnancy advanced and rose to previous levels after delivery. In other words there was an increase during pregnancy of some antidiuretic factor other than pitressin. Finally, as a result of body changes in sodium, potassium and water during pregnancy which they observed to parallel the changes in aldosterone excretion, Venning *et al.* (1959) suggest a causal relationship.

As to the effects of the blood volume changes, these assist the course of normal pregnancy. There is a decrease in blood viscosity. This permits the increase in blood flow known to occur in pregnancy, without putting additional strain on the mother's heart, and contributes to the easy exchange of gases and solutes between mother and fœtus. In particular the maternal skin blood flow is greatly increased (Burt, 1950) and this and the increase in blood volume serve to get rid of metabolic heat from the products of conception (Hytten and Duncan, 1956). The increase of blood and extravascular fluid provides a reserve against undue hæmorrhage at parturition, so that the pregnant woman can withstand much greater loss of blood than the non-pregnant.

Incidence of Anæmia in Pregnancy

Generally speaking the incidence of anæmia in pregnancy parallels but is higher than the incidence of anæmia in the general population. While accepting that hæmodilution causes a reduction in hæmoglobin concentration in pregnancy and that this is not a true anæmia, it must be admitted that the incidence of true anæmia in pregnancy is high in most parts of the world. Any attempt to determine this incidence presupposes an accurate definition of the non-anæmic state and this has not yet been agreed upon in the non-pregnant woman far less in the pregnant.

Text-books give as the normal range of hæmoglobin concentrations something like 14–17 g./100 ml. (96–116%) for men and 12–15·5 g./100 ml. (82–106%) for women. In Report (1945) the average figures for apparently healthy men and women are 15·1 g./100 ml. (103%) and 13·7 g./100 ml. (94%) respectively, and such differences between the sexes are widely accepted. However, a

hæmoglobin concentration which can be raised by iron therapy or diet is not normal. Witts (1962) suggests that this is not so, and that iron in therapeutic doses stimulates the bone marrow and causes a rise in hæmoglobin concentration in normal subjects, but the evidence of this is equivocal. Thus Verloop et al. (1959) claim to have shown that this is so. However, their series was very small and appears to have included anæmic subjects. Thus serum iron levels were as low as 82 and 83 μg/100 ml., and tended to be low particularly in the women. The women started with hæmoglobin concentrations 2 g./100 ml. lower than the men, showed greater iron absorption and a somewhat higher rise in hæmoglobin concentrations despite the short period over which observations were made. Even so, the rise in hæmoglobin concentrations in men was no greater than the accepted diurnal variation and was not statistically significant. Garry et al. (1954) have also claimed to have shown that iron therapy raises the hæmoglobin concentration in normal subjects. However, what they did show was that physiology students show a fall in hæmoglobin concentration of about 0·55 g./100 ml. during that very intensive year of their studies and that small doses of iron lessen but do not abolish this fall. Their conclusion that iron raises the hæmoglobin in normal subjects does not seem tenable. Of importance in this connection is the work of Peterson and Ettinger (1953) on hæmochromatosis. They showed that the increased iron absorption which occurs in this condition is not accompanied by any acceleration in the rate of erythropoiesis.

In the absence of anæmia the rate of erythropoiesis is controlled by erythropoietin. This subject cannot be discussed in great detail here and interested readers are referred to Symposium (1960). Erythropoietin occurs in two forms. One is a heat-stable lipid which stimulates red cell production without increasing hæmoglobin production. The other is a heat-labile mucoprotein which stimulates hæmoglobin production. The level of plasma erythropoietin is determined by the relationship between oxygen supply and tissue metabolic needs. Thus it increases and the hæmoglobin concentration and red cell count rise in such hypoxic states as living at high altitudes, chronic bronchitis and emphysema, and chronic cardiac insufficiency. The stimulus to increased bone marrow activity which occurs in hæmolytic anæmias, deficiency anæmias under therapy, and acute hæmorrhage is due to the increase in plasma erythropoietin present under these conditions. Polycythæmia vera is accompanied by an idiopathic increase in plasma erythropoietin. As would be expected, increased erythropoietin has been shown to

occur in cord blood and in the blood of pregnant animals. It seems probable that the increase in red cell volume and total hæmoglobin mass in pregnant women will be shown to be due to an increase in plasma erythropoietin. It has not been shown that the administration of iron causes an increase in erythropoietin, and for the present it cannot be accepted that iron will raise the normal hæmoglobin concentration to above normal levels.

Widdowson and McCance (1936) were unable to raise the hæmoglobin levels in normal men by iron therapy, but were able to raise them in apparently normal women to levels equalling those of men. Yudkin (1944) showed that entrants into the Women's Auxiliary Air Force had normal *women's* hæmoglobin concentrations, but that 6 months later, after being on a diet high in iron content, they had normal *men's* hæmoglobin concentrations. Such differences as there are between the normal hæmoglobin concentrations of men and women, as opposed to those of apparently healthy men and women, occur at a much higher level than that usually accepted, are more or less negligible in degree and are probably due to differences in plasma volume rather than total hæmoglobin mass, under the influence of their differing sex hormone status. Women entering pregnancy with hæmoglobin levels significantly below the range accepted as normal for men must be taken to be anæmic.

Since hæmodilution of pregnancy is very variable it is impossible to apply to the individual patient the tables of normal hæmoglobin concentrations in pregnancy which have been compiled at various times, nor some arbitrary figure such as 10 g./100 ml., to decide whether or not she is anæmic. The application to a group of subjects of some such figure is not an accurate measure of the frequency of anæmia either. In this case figures such as those in Report (1945), which are given in Table 32 are of value since they can be applied to the appropriate stage of the pregnancies of the group being studied. However, while realizing that it is not in itself a measure of the incidence of anæmia, the proportion of pregnant women who, *at first attendance at the antenatal clinic*, show a hæmoglobin concentration below 10 g./100 ml. can be used to compare the frequency and severity of anæmia among different groups and at different times.

Thus it has been shown that in the United Kingdom some 10–20% of women show a hæmoglobin concentration of less than 10 g./100 ml. at that time, and that this percentage is falling (Scott, 1962b). In the United States the figure approximates to that in this country, negroes showing a higher incidence of anæmia than whites. In Eire

Table 32

HÆMOGLOBIN LEVELS IN COURSE OF PREGNANCY
(100% = 14·6 g. per 100 ml.)

Duration of pregnancy (calendar months)	1	2	3	4	5	6	7	8	9
Average hæmoglobin per cent	90·6	89·1	89·3	85·4	86·2	82·2	81·6	81·7	82·7
Mean per trimester		89·12			86·26			82·38	

the figure tends to be higher, although here also there has been some improvement in recent years. In tropical countries the incidence is very high indeed, so much so that it is frequently reported in terms of a lower hæmoglobin concentration than 10 g./100 ml. In Australia the incidence of anæmia is probably the lowest in the world.

Poverty is undoubtedly the most important social factor in the causation of anæmia. There are, however, others which are important. War and the shortages and rationing which it entails, particularly when it is being lost, has its effects, as Roscoe and Donaldson (1946) have shown in comparing hæmoglobin levels in the lean year of 1942 with those in the fatter year of 1944. But war cancels out the effects of poverty on the incidence of anæmia in pregnancy, for such things as availability, price control, rationing and propaganda have the result that wide sections of the community eat more or less similar diets.

The social and medical services provided by the State, as well as the full employment of the post-war years did much towards the eradication among pregnant women of severer degrees of anæmia, in this country. The figures given by Young *et al.* (1946) may be compared with those for St. Andrew's Hospital in 1954, both relating to women in the first 24 weeks of pregnancy (Fig. 8). It is seen that, while the earlier series showed an incidence of 12·5% of hæmoglobins below 70% (10·2 g./100 ml.) the comparative incidence in the later series was 6%. It should be appreciated that St. Andrew's Hospital serves a poor-class population in the East End of London and it is unlikely that nutritional standards here are higher than those in other parts of London. Fig 8 also shows the distribution of hæmoglobin concentrations among women at their first attendance at the antenatal clinic in 1960. As can be seen there was some regression. The incidence of hæmoglobins below 10·2 g./100 ml. was now about 9% and the general picture resembled that of the 1945 series. We believe that the explanation lies in the increasing number of immigrants from the West Indies and India in particular in this area, and have observed a high incidence of intestinal parasitism among such patients. Other factors of minor importance in Western countries but of major importance in many tropical countries are racial, religious and sectarian prejudices in the field of diet. Personal prejudice and lack of education in the field of dietetics must also be taken into account and may result in a poor intake of essential substances. It is of interest to note that Report (1945) points out that, *among women suffering no financial restrictions*, the average daily intake of iron was 11·4 mg. and that 30% had an average daily intake of less than 10 mg.
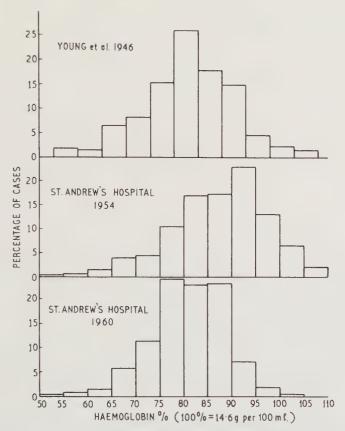
FIG. 8. Comparison of hæmoglobin levels in pregnancy in 1946, 1954 and 1960.

Classification of Anæmias

The primary requirement for correct treatment is correct diagnosis and for this some form of classification is required. The treatment of anæmia without diagnosis and the trial-and-error method of changing from one hæmatinic or route of administration to another are to be deplored. The following classification is intended as a guide only. Many cases are mixed and many will not fulfil the criteria which follow. The opinion of a hæmatologist should not be dispensed with.

Hæmorrhagic Anæmias: (*a*) Acute. (*b*) Chronic.

Deficiency Anæmias, e.g. iron, folic acid, vitamin B_{12}.

Hæmolytic Anæmias: (*a*) Familial. (*b*) Acquired. (*c*) Infective and toxic.

Anæmias of Bone Marrow Insufficiency: (*a*) Aplasia, hypoplasia and neoplastic displacement of bone marrow. (*b*) Toxic inhibition of erythropoiesis.

Consideration will be given here to those anæmias in pregnancy which have attracted most attention, iron deficiency anæmia, megaloblastic anæmia of pregnancy and the hæmolytic states associated with the abnormal hæmoglobins, particularly hæmoglobin-S.

Iron Metabolism

The Ingested Iron. Iron is normally ingested in the form of food. Many studies of iron metabolism have been made using simple inorganic iron salts, often in unphysiologically high dosage and many of the results obtained do not apply to the absorption of food iron. The maximum quantity of iron normally available from food is 2–4 mg. per day (Finch, Haskins and Finch, 1950).

Much of the iron in food is in the ferric form, generally in organic compounds, although some, including that of hæmoglobin, is in the ferrous form. Contrary to previous belief the iron of hæmoglobin is available for absorption to a degree at least equal to that of other foodstuffs. Food iron is converted by the processes of digestion to simple ferrous compounds before absorption, reducing substances such as ascorbic acid assisting in this process. The absorption of ferric salts is poor. Hæmoglobin is probably absorbed as hæm.

Hydrochloric acid may play a part in the preparation of food iron for absorption but is not essential. Thus it is common experience that patients with Addisonian pernicious anæmia are not necessarily iron deficient. Earlier work indicated that there is no diminution in iron absorption in achlorhydric subjects, that the administration of hydrochloric acid to patients with achlorhydria does not increase their iron absorption and that iron deficiency causes increased iron absorption even in achlorhydrics. This work has recently been verified by Biggs *et al.* (1961). They showed that food iron was equally absorbed by non-anæmic subjects whether they were achlorhydric or not. This applied also to anæmic subjects, but at a higher level of absorption. The concurrent administration of considerable quantities of normal gastric juice did not increase iron

absorption in achlorhydric subjects. The classical work of Strauss and Castle (1932, 1933) cannot therefore now be accepted. They suggested that the frequent occurrence of hypochlorhydria and achlorhydria in pregnancy was a factor in the causation of iron deficiency anæmia. It is now believed that the reverse is the case; that iron deficiency is responsible for the changes in the gastric mucosa from superficial gastritis to complete atrophy which are responsible for the hydrochloric acid deficiency. It has been shown that iron therapy will, in many cases, resolve these pathological changes with a return of hydrochloric acid secretion (Smith, 1959). Nevertheless, the question is not yet entirely settled and recent work has not always verified these findings.

However, even if hydrochloric acid is not essential for the absorption of iron it appears that some process which occurs within the stomach is. Thus Pirzio-Biroli *et al.* (1958) demonstrated that partial gastrectomy reduces the absorption of food iron by half. It seems likely that this is due to the rapidity with which food is released into the duodenum after partial gastrectomy.

The absorption of iron from food is about half of that from simple iron salts, and the administration of iron salts with food reduces their absorption considerably. In part at least, this is due to the dietary content of phytates and phosphates which form insoluble, unabsorbable compounds with iron. This is of particular importance in tropical countries where the diet may contain large quantities of these substances. It has however been shown (Turnbull *et al.*, 1961) that neither food nor phytate reduce the absorption of hæmoglobin iron. In fact they increase it.

It is accepted that the reduction of iron to the ferrous form is effected by reducing substances such as ascorbic acid and that these increase the absorption of food iron. Ascorbic acid has no effect, however, on the absorption of hæmoglobin iron (Turnbull *et al.*, 1961).

The Absorption of Iron

Under normal circumstances iron is absorbed almost entirely from the immediately post-pyloric duodenum. In iron-deficiency anæmia and when the duodenum is by-passed as in gastroenterostomy the absorptive capacity of the more distal small intestine increases. However, it never reaches that of the duodenum and can cope only with physiological doses of iron. An alkaline medium, in which iron salts are less soluble, reduces absorption and it has been shown in this connection that pancreatic damage increases iron absorption.

There has been a considerable recent change in our views on the mechanism of iron absorption. Earlier work suggested that ferrous ions diffuse into the cells of the mucous membrane of the duodenum and stimulate the production within these cells of a protein, *apoferritin*. The ferrous ions, oxidized to the ferric form, combine with the apoferritin to form *ferritin*. The combined iron is slowly released, crosses the cell membrane as ferrous iron into the circulation and, again re-oxidized, combines with a β-globulin known as *transferrin* or *siderophilin*, thus becoming the plasma transport iron. The freed apoferritin becomes available for further iron absorption.

From this theory there developed Granick's (1946) "mucosal block" theory of the control of iron absorption. Since there is virtually no loss of iron from the body, and what slight loss there is does not vary significantly in conditions of iron depletion or iron excess, there must be control of absorption. Granick's mucosal block theory postulated that this control is effected by the ferritin mechanism within the cells of the duodenal mucous membrane in that, when it is saturated, absorption temporarily ceases. However, it soon became apparent that this theory could not answer all the facts. For example, Smith and Pannacciulli (1959) showed that in normal subjects increasing the dose of oral iron in stages from 0·001 mg. to 100 mg. steadily increases the iron absorption from 0·0003 mg. to 12·6 mg. They stated that there is no limit to the total amount of iron which will be absorbed and that there is therefore no mucosal block.

Recent work has served to clarify the position. Brown and Rother (1961) instilled iron into the duodenum of normal rats. In the first 15 minutes, within the mucosal cells, little if any of the absorbed iron became bound to protein. Thereafter, the bulk of the absorbed iron became bound to protein while the rest migrated across the cell in combination with serine and glycine. In iron-deficient rats the association between iron and serine and glycine persisted, as did the iron absorption, and there was little binding of iron to protein within the mucosal cells. Charlton *et al.* (1963) verified these observations. They showed that during the first hour after a dose of iron, while iron absorption is most active, the ferritin-bound fraction increases (i.e. is not being absorbed) while the non-ferritin fraction decreases (i.e. is being absorbed). The ferritin fraction then remains constant until it diminishes as the mucosal cells are shed. They showed further that in iron-overloaded animals oral iron causes a rapid rise in ferritin within the mucosal cells

followed by a slow fall as the mucosal cells are shed, without any corresponding absorption of iron. Similarly, they demonstrated rapid absorption of oral iron in iron-deficient rats, without any ferritin production. In other words, there is control of iron absorption by a ferritin mechanism within the cells of the duodenum. Such iron as combines with apoferritin is not absorbed, but is shed with the effete mucosal cells. Iron which does not combine with apoferritin is absorbed. When the uncombined siderophilin level in the plasma is high (as occurs in iron deficiency and in states of increased erythropoiesis) there is rapid acceptance of iron from the mucosal cells and little binding to apoferritin. When there is iron repletion and the uncombined siderophilin level in the plasma is low iron is accepted slowly from the mucosal cells and much becomes bound to apoferritin and in due course is released back into the gut. There is therefore a mucosal block but the mechanism is not that postulated by Granick, and it can be appreciated that this mechanism may only be partly effective when large doses of iron are given.

Nevertheless, the mechanism exerts considerable control over iron absorption. While it is true that in Smith and Pannacciulli's experiments in normal subjects increasing the dose of iron was accompanied by an absolute increase in iron absorption, nevertheless the proportion absorbed fell from 33% at low dosage to $12 \cdot 5\%$ at high dosage. In iron-deficient subjects they found that, irrespective of the dose of iron, its absorption remained fairly constant at about 50%. Bannerman *et al.* (1962) obtained essentially similar results in rats. In iron-deficient rats there was 70–80% absorption of iron irrespective of the dose. In iron-replete rats the proportion absorbed fell from $26 \cdot 5\%$ at low dosage to $4 \cdot 8\%$ at high dosage. The ferritin mechanism therefore ensures that there will be maximal absorption of iron in iron deficiency, and minimal absorption in iron repletion. Under natural conditions, when the total amount of iron offered with a single meal is no more than about 5 mg. this mechanism is effective in preventing over-absorption of iron.

The plasma level of uncombined siderophilin and the rapidity with which iron is liberated to the bone marrow and body stores from siderophilin will exert a controlling influence over the ferritin mechanism. In iron-deficiency anæmia there is an increase in free siderophilin. In conditions of increased erythropoiesis, such as occurs in hæmolytic conditions, there will be rapid release of iron from siderophilin to the bone marrow. Under these circumstances the plasma will accept iron more rapidly from the duodenal mucosal

cells, ferritin production will be minimal and the absorption of iron will be increased. It can now be understood why the first evidence of iron-deficiency is an increase in iron absorption, even before there is a reduction in iron stores.

Succinic acid, ascorbic acid and other reducing substances, even those without any known metabolic function (Pollack *et al.*, 1963), increase the absorption of iron. It has been suggested therefore that the intracellular oxidation-reduction potential of the duodenal mucous membrane is of importance in the control of iron absorption.

Hæmoglobin iron does not seem to be absorbed by the same serine-glycine mechanism as other food iron, but rather as the iron-porphyrin complex hæm (Turnbull *et al.*, 1961). As has been pointed out, its absorption is unaffected by the presence of ascorbic acid, and increased rather than decreased by the presence of phytates.

Abnormalities of the mucous membrane result in abnormalities of absorption. Thus in the malabsorption syndrome the changes in the mucosa of the small gut are accompanied by diminished iron absorption which is not increased by iron deficiency.

The Transport of Iron

The iron in the plasma is in the ferric form, attached to the β-globulin siderophilin. It totals about 4 mg., and under normal conditions 20–26 mg. of iron leave the bloodstream daily, so that there is a turnover of plasma iron five or six times a day.

Serum iron estimations are being increasingly requested for the diagnosis of the nature of anæmia. However, the factors which control the serum iron level are complex, and it is not necessarily a measure of the degree of iron deficiency or repletion of the body. The normal serum iron is about 100 μg./100 ml. The total iron-binding capacity of the serum, a measure of the siderophilin level, is about 300–350 μg./100 ml., so that there is normally about one-third saturation of the T.I.B.C. In connection with what has been said of the "normal" hæmoglobin concentrations of men and women, it is of interest to note that the "normal" serum iron levels are lower in women than in men. The serum iron and siderophilin levels to be expected in various conditions are illustrated in Fig. 9, taken from the work of Nussbaum (1959). In pregnancy, even in the absence of iron deficiency, there is a rise in siderophilin level (Lowenstein *et al.*, 1960).
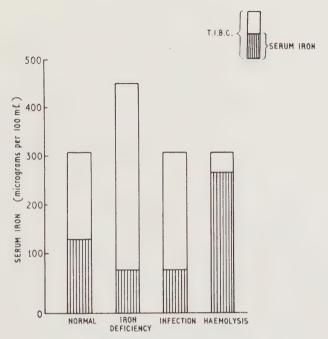
FIG. 9. Serum iron and iron-binding capacity.

The serum iron level is lowered by:

1. Malabsorption or inadequate intake of iron.
2. Depletion of body iron by chronic hæmorrhage.
3. Increased deposition of iron in the tissues as in sepsis.
4. Rapid synthesis of hæmoglobin as in hæmorrhage or megaloblastic anæmia under treatment.

The serum iron level is raised by:

1. Overloading of iron stores as in hæmochromatosis and transfusion siderosis.
2. Hæmolysis.
3. Reduction of hæmoglobin synthesis not related to iron deficiency as in megaloblastic anæmia in relapse.
4. Abnormal liberation of iron as in liver disease with disruption of cells.

The Storage of Iron

The normal amount of iron stored in the body is variously estimated at between 600 and 1,500 mg., sufficient to replace the loss of up to 3 pints of blood. The main stores are the liver, spleen and bone marrow. Normally about two-thirds is stored as water-soluble ferritin, containing 17–23% of iron, and the remainder as insoluble hæmosiderin, containing 35%. When storage iron is excessive, as in hæmochromatosis, transfusion siderosis, hæmolytic anæmia and the over-enthusiastic administration of parenteral iron, the excess is deposited as hæmosiderin. Such deposits cause hæmosiderosis. While this condition is usually benign, it does not always appear to be so, and may progress to a true hæmochromatosis (Williams and Pitcher, 1963). This may occur in such conditions as thalassæmia and sickle-cell disease. It appears that it is the iron which is absorbed from the gut and not that released by hæmolysis or the breakdown of transfused blood which is responsible for the tissue damage which ensues. However, the iron released from transfused blood, hæmolysis and possibly parenteral iron, may cause a redistribution of absorbed oral iron and so accelerate the development of hæmochromatosis.

The simplest way to assess the body iron stores is to examine the bone marrow for hæmosiderin, which is reduced in iron deficiency and present in excess when there is excessive iron storage.

The speed with which iron will appear within the erythrocyte depends on the state of iron metabolism. It is much more rapid in the iron deficient than in the normal subject, for the body will store very little iron while there is a deficiency of hæmoglobin due to iron lack.

There is a considerable body of opinion that, in the presence of a normal hæmoglobin level, the absorption of oral iron reverts to normal and that parenteral iron becomes necessary to replenish iron stores. There is, however, considerable evidence to the contrary, although, understandably, the absorption may not be as great as in iron-deficiency anæmia. Thus it has been demonstrated on a number of occasions that there is increased absorption of iron in pregnancy in the absence of anæmia. Since there is accelerated erythropoiesis in pregnancy (Pritchard and Adams, 1960), even in the absence of anæmia, this is not unexpected. In addition, Steinkamp *et al.* (1955) were able to use increased absorption of iron to demonstrate the existence of iron deficiency without anæmia in non-pregnant subjects.

Widdowson and McCance (1948) investigated the influence of sex hormones on the storage of iron. In animal experiments they showed that with the onset of sexual maturity the female stores more iron than the male and that removal of the gonads causes an increase in iron storage in the male and a decrease in the female. Stilbœstrol causes some reversion towards the higher level in the spayed female. One would like to explain the phenomenon as a preparation for the iron demands of pregnancy but unfortunately it does not occur in all animals.

Tissue Iron

Knowledge of tissue iron is very incomplete, but it may be said that tissue iron deficiency occurs in iron deficiency anæmia and results in a fall in certain iron-containing enzymes. This is responsible for such changes in anæmia as koilonychia, glossitis and dysphagia. Degenerative changes occur in the epithelial tissues of anæmic patients and these will respond to iron therapy. It has been demonstrated that there is a fall in the cytochrome and catalase levels in the liver and spleen in iron deficiency anæmia.

The Utilization of Iron for Hæmoglobin Synthesis

Iron is incorporated into the hæm radicle for the production of a number of substances responsible for oxygen transfer, including hæmoglobin, the cytochromes, catalase and peroxidases. The iron made available by the reticuloendothelial system from hæmoglobin breakdown or parenteral administration is used in preference to store iron for hæm synthesis. There is thus little turnover of store iron in normal subjects. With regard to oral iron, Callender (1962) has shown that in normal subjects 70% of the absorbed iron is used in the next 10–14 days for hæmoglobin synthesis, the remainder going into the body stores or possibly being used for enzyme synthesis. In iron deficient subjects almost all of the absorbed iron appears in new erythrocytes in a few days.

In an adult with a hæmoglobin concentration of 14·6 g./100 ml. (100%) there is a total of 750–900 g. of circulating hæmoglobin, representing 2·5–3 g. of iron. In iron deficiency anæmia the amount of iron to be given, and in hæmorrhagic anæmia the amount of iron to be absorbed and to be mobilized from iron stores, may therefore be considerable. In general, a rise of 1% in the hæmoglobin concentration will require about 25 mg. of iron. In other words, 100 mg.

of utilized iron will cause a rise of a little less than 0·6 g. of hæmoglobin per 100 ml. of blood. At the same time large quantities of amino-acids are required for globin synthesis and this may become an important factor in the production of anæmia in chronic protein deficiency. A deficient intake of protein, however, is almost invariably accompanied by a deficiency in other factors such as vitamin C, folic acid and vitamin B_{12} and the deficiency of these usually becomes apparent, in terms of the onset of anæmia, long before the protein deficiency.

The liberation of iron from the body stores is stimulated by a lowering of the oxygen tension of the tissues and blood. Thus, in hæmorrhagic shock the hypoxia is sufficient to release enough iron from the body stores to saturate almost completely the iron-binding capacity of the plasma (Green and Mazur, 1956). As has been pointed out, hypoxia causes an increase in plasma erythropoietin and this stimulates increased red cell and hæmoglobin production.

The released iron is utilized for hæmoglobin synthesis within cells of the red cell series by reactions which involve reducing agents such as ascorbic acid, and the processes of purine metabolism. These reactions are enzymatically controlled and occur only in nucleated red cells and, to a lesser extent, reticulocytes. They do not occur within mature red cells, which lack the necessary enzymes. The iron is accepted initially by the red cell stroma and then transferred to the cytoplasmic protoporphyrin for hæm synthesis. In certain conditions, such as lead poisoning, this transfer is blocked and red cell protoporphyrin is present in excess (Goldberg, 1959; Falbe-Hansen and Lothe, 1961).

The Causes of Iron Deficiency Anæmia in Pregnancy

Approximately 500 mg. of iron are required in the course of pregnancy for the increase in maternal tissues and the development of the products of conception. Most of this is needed late in pregnancy. There is a variable loss of iron to be met in the hæmorrhage which accompanies parturition, and lactation accounts for a further 150 mg. In all, the additional iron requirements of pregnancy total about 900 mg. The menstruating female loses about 50 ml. of blood, or 25 mg. of iron each month, a total of about 250 mg. of iron during the duration of a normal pregnancy. The pregnant woman therefore requires about 650 mg. of iron over and above her normal needs, or about 500 mg. if she does not breast-feed her baby.

In addition she requires, on average, a further 500 mg. for the increase in circulating hæmoglobin mass, although, as has been shown, this figure is very variable indeed. This iron, however, is not lost from the body and will be returned to the body stores in the puerperium. When, however, a woman enters pregnancy with iron deficiency, as 11 out of 12 women do (Holly and Grund, 1959), this demand must be met from the diet.

The pregnant woman must replace the normal loss of 1 mg. or so of iron in fæces, urine and skin. If she is a young person she must find the extra iron required for the increase in body stores and blood space which accompanies her natural growth. At the age of 17 this is about 270 mg. during the course of pregnancy, falling thereafter to zero at about the age of 21. This can be an important factor in the causation of anæmia among races where frequent pregnancies before the age of 21 are the rule.

The losses during menstruation may be very much greater than that indicated above, and such menorrhagia may be completely unsuspected by the patient. Thus Hagedorn *et al.* (1961) report an unsuspected menorrhagia of 254 and 361 ml. in consecutive menses. They point out that among 12 non-anæmic women the average menstrual blood loss was 27 ml., while among 15 iron-deficient women it ranged from 103 to 579 ml.

The non-pregnant iron requirements, normally estimated at about 2 mg. per day, may in fact be much greater than this and when it is remembered that of the 15 mg. in a good mixed diet only 3 or 4 mg. are absorbed by an *anæmic* subject, it becomes apparent why so many women enter pregnancy with inadequate iron reserves if not frank anæmia. It becomes apparent also why most women, unless they are given iron supplements, develop progressive anæmia during pregnancy.

The causes of iron-deficiency anæmia in pregnancy are:

Deficient Intake of Iron. In pregnancy 16–20 mg. of iron are required in the diet per day. Poverty, ignorance and prejudice have been mentioned as factors causing deficient iron intake, as has the influence of excess phytates and phosphates on the availability of dietary iron. In addition, vomiting and impairments and abnormalities of appetite may occur in pregnancy and these will also diminish iron intake, as will the toxæmia of any intercurrent infection.

Deficient Absorption of Iron. Lesions of the alimentary canal such as those which occur in the malabsorption syndrome are accompanied by deficiency in the absorption of iron. Intestinal hurry due

to intercurrent infection, dietary indiscretion or intolerance to the dosage and form of oral iron medication will also diminish iron absorption.

Increased Demands for Iron. In addition to the demands of pregnancy itself, other demands may occur. Thus infection causes an increased demand for iron by the tissues and retards the response of anæmia to iron until it is treated. Giles and Brown (1962) found urinary infection to be twice as common in anæmic as in non-anæmic pregnant women on routine supplements of iron and folic acid. Hæmorrhage results in a loss of iron, and the writer has now collected a number of cases of iron-deficiency anæmia in pregnancy who failed to respond satisfactorily to treatment, in whom there was evidence of peptic ulceration. Similarly, he has found the incidence of ankylostomiasis to be high among anæmic pregnant women who have recently immigrated from tropical countries.

Inhibition of Bone Marrow. Infections and intoxications divert iron to the tissues and depress bone marrow activity and iron absorption. It is unlikely, however, that these could by themselves cause severe or progressive anæmia.

It should be noted that, although the demands for iron in an uncomplicated pregnancy are increased they are not so great as to cause severe anæmia in a normal woman. If such an anæmia is present it must have been present before conception, or there must be some complication of the pregnancy.

Diagnosis

The diagnosis of well-established iron-deficiency anæmia is simple and can generally be made by estimating the hæmoglobin concentration and examining a stained film of the peripheral blood (Figs. 10 and 11) for hypochromia. Scott (1962b) points out that anisocytosis occurs in anæmia and not in pure hæmodilution, and serves to differentiate them when the anæmia is not sufficiently severe for hypochromia to be significant. In doubtful cases a low mean corpuscular hæmoglobin concentration is diagnostic. In very mild cases and in demonstrating subclinical iron-deficiency states the oral iron tolerance test may be used (Kuenkel *et al.*, 1954). It must however be borne in mind that this test is also "positive" in conditions of increased erythropoiesis with increased iron absorption, such as occur in normal pregnancy without anæmia, and this must be allowed for in the interpretation of results. A sensitive test for iron deficiency is the percentage of sideroblasts in the bone marrow.
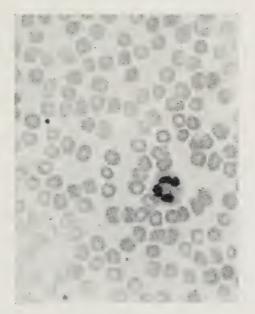
Fig. 10. Normal blood film.
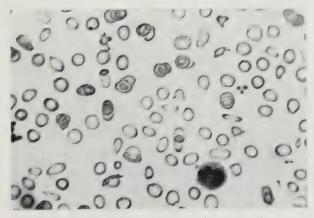
Fig. 11. Blood film of iron deficiency anæmia.

In significant iron deficiency these comprise less than 10% and in iron sufficiency more than 20% of nucleated red cells.

Deficiency of storage iron is best demonstrated by staining sections of bone marrow fragments for iron.

Treatment

In view of what has been said many workers have advised routine oral iron therapy in all pregnant women, whether they are considered to be anæmic or not. The major exception, the presence of hæmolytic anæmia, will be discussed later. In support of this recommendation is the work of a number of authors who have clearly shown that the administration of routine oral iron means that women complete pregnancy with higher hæmoglobin concentrations, higher levels of bone marrow iron, higher serum iron levels and higher mean corpuscular hæmoglobin concentrations than if iron is not given.

Whether it need be given to the 1 in 12 women who enter pregnancy without anæmia is, however, debatable. Such women must obviously be on an adequate diet and, in the absence of complications, will complete pregnancy without significant anæmia, if any at all. However, the decision as to whether a woman is anæmic or not must not be based on some figure such as a hæmoglobin concentration of 10 g./100 ml., as the dividing line between normality and anæmia. The earlier discussion on this point makes it clear that a more appropriate level would be 14·6 g./100 ml. (100%). Nevertheless, the prescription of iron to such women is unlikely to do harm. The control of iron absorption will continue to be effective and after the pregnancy, when iron therapy is discontinued, will still continue to be effective and so allow the gradual elimination from the body stores of the excess iron deposited during the destruction of the extra hæmoglobin which was created during the pregnancy. Theoretically, when pregnancies in such a case follow rapidly on one another, hæmochromatosis might result and the careful practitioner might decide to withhold routine iron. This is however theoretical, no such cases have been reported and its occurrence is unlikely in the extreme.

It is not necessary to discuss here such things as rest, diet and the treatment of cause in established iron-deficiency anæmia. Discussion will be confined to some general principles in the use of iron.

Other iron preparations are usually compared with ferrous sulphate, in its commonest form a green, coated 3 gr. (0·2 g.) tablet

containing 1 gr. (0·06 g.) of ferrous iron, with a little copper and manganese, and usually prescribed as one tablet three times a day. The advantages of this preparation are its cheapness and the fact that the iron is in the ferrous form. It has often been stated that the various iron compounds have their own indices of absorption and that for ferrous sulphate this is 14%. In other words, of a dose of ferrous sulphate 14%, or about one-seventh, will be absorbed. This is not so. The percentage absorption is controlled by the state of iron metabolism of the patient and, in non-anæmic subjects, by the dose of iron. An iron-deficient subject will absorb more than a normal subject and, on the whole, the more severe the deficiency the greater will be the absorption. Absorption will also be influenced by intestinal hurry, toxæmia and so on. Iron is often taken after meals and this will tend to reduce absorption. Ascorbic acid will increase it. Nor is it true to say that there is any difference in the absorption of various ferrous salts. Such claims are generally based on observations in which comparable doses of iron were not used. A number of workers (O'Sullivan *et al.*, 1955; Gatenby and Lillie, 1955; Gatenby, 1959) have shown that, if strictly comparable doses in terms of iron content are used, there are no significant differences in the absorption of iron from a range of ferrous salts and chelated iron compounds. Simple ferric salts are poorly absorbed. There are however reports in which comparable doses of different iron preparations gave different responses. For example, Holmes (1957), showed that 150 mg. of iron per day produced a greater increase in hæmoglobin concentration in pregnant women when given as ferrous calcium citrate than 200 mg. per day given as ferrous sulphate. However, no intolerance was encountered among the patients on ferrous calcium citrate, whereas the intolerance rate among those on ferrous sulphate was 44%. Since the symptoms of intolerance include nausea, vomiting and diarrhœa it is not unexpected that in the group on ferrous sulphate absorption would be subnormal. This does not mean however that, other things being equal, ferrous calcium citrate is better absorbed than ferrous sulphate.

The comparison of the hæmatinic effect of iron compounds in pregnant women is also complicated by the very variable dilution which occurs, if the hæmoglobin concentration is used as the yardstick of comparison. Vogel *et al.* (1963) have shown that groups of pregnant women who appear to be comparable in terms of their hæmoglobin concentrations, may be anything but if one examines their mean corpuscular hæmoglobin concentrations. They also found

that responses to different iron preparations may differ widely if hæmoglobin concentrations are used as the yardstick of comparison, but become similar if mean corpuscular hæmoglobin concentrations are used.

Intolerance is an important problem in oral iron therapy. The symptoms most commonly encountered are nausea, vomiting, abdominal discomfort, constipation or diarrhœa, pruritis ani and accentuation and inflammation of hæmorrhoids. Such intolerance is particularly frequent in pregnancy and may approach an incidence of 50% with the use of ferrous sulphate. Much lower intolerance rates are reported for ferrous gluconate, ferrous succinate, ferrous calcium citrate and ferrous fumarate. Many deaths in children taking ferrous sulphate tablets in mistake for sweets have been reported (Lovel, 1958), and D'Arcy and Howard (1960) have verified that, in dogs, ferrous sulphate is considerably more toxic than other iron preparations. Such observations must influence the practitioner in his choice of iron preparation and must outweigh the question of cost.

However, the question of intolerance to ferrous sulphate is very interesting. Two factors appear to operate in determining the onset of symptoms of intolerance, the irritant and toxic properties of the salt itself, and a strong psychological factor. With regard to the former, the dose employed becomes important. Most series with high intolerance rates have been in patients taking doses of 300 mg. or more of iron per day. The writer is aware of an increasing tendency to prescribe six tablets of ferrous sulphate (about 360 mg. of iron) per day. Such high doses are unnecessary and are accompanied by high intolerance rates, with consequent poor absorption in affected subjects. Brumfitt (1959) successfully treated iron-deficiency anæmia in males with one tablet of ferrous sulphate twice daily and observed no cases of intolerance. As has been shown, at least a 50% absorption of iron can be expected in iron-deficiency anæmia. This being so, Brumfitt's patients were absorbing no less than 60 times the daily iron needs of a normal male. Had they been anæmic pregnant women they would have been absorbing at least 10 times the normal daily iron needs of pregnancy.

With regard to the psychological factor, three series of observations are worth describing. Egdar and Rice (1956) showed that the substitution of white for green ferrous sulphate tablets reduced the incidence of intolerance in pregnant women to 6%, and Girdwood (1952) found that 14 out of 16 patients intolerant to coloured ferrous sulphate tablets tolerated identical white tablets. Kerr and

Davidson (1958) showed that in small but adequate doses there is no difference between the intolerance rates of a series of ferrous salts including ferrous sulphate and an "unknown" control tablet (lactose) imagined by the subjects to be an iron preparation. "Known" tablets of lactose, however, caused virtually no intolerance.

Parenteral Iron

In recent years relatively non-toxic parenteral preparations of iron have been introduced. The total dose of these can be calculated and be seen to be given. Apart from any loss in the urine after each injection there is virtually complete absorption in due course and this is not affected by gastrointestinal disease, dietary factors or intolerance. In addition, the reduction in the absorption of oral iron which accompanies improvement in the anæmia is not a problem with parenteral iron, which is also a more rapid method of replenishing body iron stores.

These are preparations of ferric iron. When injected most or all of the dose is taken up by macrophages and slowly liberated into the bloodstream. It is to this slow release and the ferric state of the iron that they owe their relative freedom from toxicity.

Intravenous Iron

Three preparations are commonly used, saccharated iron oxide, iron dextrin and iron dextran. It is essential, in order to minimize the possibility of reactions, to start with small doses, working up to full dosage in two or three days, and to inject the preparation slowly. Except when it is used in high dilution, the administration of iron dextran appears to be accompanied by the highest incidence of reactions (Fielding, 1961). Its intravenous use is most frequently therefore by the total dose technique. In this the total dose calculated to be necessary (the manufacturers give the necessary information on how this calculation is made) is given in a slow infusion. It is given as a 5% solution in physiological saline over a period of 4–12 hours. Originally it was suggested that it be administered in 5% glucose, but this resulted in a high incidence of thrombophlebitis in the veins used, and the substitution of saline was found to eliminate this (Humphrey, 1964).

The iron-dextran must be added to the diluent with aseptic precautions for the mixture cannot be autoclaved. Contamination with alcohol, detergents and strong electrolytes, which also tend to

precipitate out the iron preparation, must be avoided. To avoid sensitization reactions it should not be given between 7 and 21 days after previous injections of iron. Other iron therapy should be discontinued at least 48 hours before the iron dextran is administered. Used in this way the method appears to be remarkably safe. The serum iron levels reached are quite astronomic, and take a month or so to revert to normal. The lack of toxicity appears to be due to the fact that the preparation contains no ionized iron and none of it combines with siderophilin.

In administering saccharated iron oxide a fine-gauge stainless steel needle and an all-glass syringe should be used. To ensure that the needle is in the vein and to buffer the solution, an equal volume of blood should be drawn into the syringe before commencing the injection. Injection should be performed slowly and take about 5 minutes. To prevent thrombosis at the site of injection it may be accompanied by some heparin or be followed by a small infusion of glucose through the same needle. The syringe and needle must be free of detergents and electrolytes. One gains the impression that many of the severe reactions reported have occurred when the technique of injection has not been as careful as that suggested.

Iron dextrin is less hæmolytic *in vitro* than either of the other two preparations and is much more stable than saccharated iron oxide in plasma. Fielding (1961) found reactions to this preparation to be infrequent and mild. Its utilization, however, is only about 60% of that of saccharated iron oxide and this must be allowed for in calculating the total dosage.

The local reactions which may occur to intravenous iron are thrombophlebitis, venous spasm and effusion of iron into the tissues. General reactions may be mild, moderate or severe.

Mild Reactions. Flushing of face, lightheadedness, weakness, mild headache, drowsiness.

Moderate Reactions. Muscular pains, severe lumbar pain, abdominal cramps, nausea, vomiting, diarrhœa, severe headache, lachrymation, chills.

Severe Reactions. Dyspnœa, coughing, oppressive chest pain, tachycardia, sweating, syncope, shock, epileptiform fits.

Reactions usually occur at once but may be delayed for up to 8 hours. They are particularly frequent in subjects not suffering from iron-deficiency anæmia, and the diagnosis must be certain before intravenous iron is resorted to. Severe respiratory distress occurs only in patients with valvular heart disease, chronic bronchitis and emphysema, severe kyphoscoliosis, pulmonary tuberculosis

and similar conditions. Reactions are relatively common in patients with chronic infection, rheumatoid arthritis, ulcerative colitis and chronic nephritis. In such cases small doses only should be given. Ross (1957) found the overall incidence of reactions to saccharated iron oxide to be $7\cdot5\%$ with 100 mg. doses and 43% with 500 mg. doses. In pure iron deficiency, with 100 mg. dosage and careful selection of cases, the incidence of reactions could be reduced to 5%. Pyrexia or toxæmic conditions raised this figure to 24%.

The treatment of severe reactions is rest, sedatives and, if vasomotor collapse persists, intravenous hydrocortisone and noradrenaline. A few deaths have been reported with saccharated iron oxide.

Intramuscular Iron

The most commonly used intramuscular iron preparations are iron dextran and an iron sorbitol citric acid complex in dextrin (which will be referred to here as iron sorbitol). Both are issued in ampoules containing 50 mg. of iron per ml. and in both a maximum daily dose of 2 ml. should not be exceeded and, certainly in the case of iron dextran, should be reached after a few days of smaller increasing dosage.

Injections may be given daily or less frequently and the site should be varied with each dose and be made deeply into muscle. In tracking back these preparations cause prolonged staining of the skin and very slow absorption. This can be avoided by injecting a little air after the solution or by creating a tortuous needle track by displacing the skin laterally before the injection.

Iron sorbitol has a much lower molecular weight than iron dextran and is absorbed much more rapidly and completely. However, unlike iron dextran, about one-third of each dose of iron sorbitol is lost in the urine and it should not be given in cases of pyelonephritis (in which it causes an increase in leucocyte excretion) and other renal conditions. Whereas iron dextran is absorbed mainly by the lymphatics, iron sorbitol absorption is largely directly into the bloodstream. Its use never results therefore in the painful lymphadenopathy which occasionally accompanies the use of iron dextran. A side effect peculiar to and not uncommon with iron sorbitol is an unpleasant metallic taste in the mouth and a loss of ability to taste food. Apart from this, reactions to intramuscular iron are infrequent and tend to be more common with unduly high

dosage, in patients with a history of allergy and in patients not suffering from iron-deficiency anæmia. The reactions most commonly met with are pain at the site of injection, pyrexia, headache, nausea and vomiting, giddiness, disturbances of hearing and vision and allergic manifestations.

Since about 6% of the dose of iron sorbitol becomes bound to plasma siderophilin it is important that adequate free siderophilin be available. Reactions will be common otherwise, and for this reason oral iron therapy should be discontinued at least 24 hours before commencing iron sorbitol (Scott, 1962a). This does not apply to iron dextran. However, reactions to iron sorbitol have been reported in patients not on concurrent oral iron. Fatalities are always rare, but have been reported with iron dextran.

The treatment of severe reactions is that suggested for reactions to intravenous iron.

Dosage of Parenteral Iron Preparations

The total dosage may be calculated in the case of saccharated iron oxide and iron dextran by allowing 25 mg. of iron for each 1% (0·146 g./100 ml.) that the patient's hæmoglobin concentration is below the level aimed at and allowing a further 25–50% of the dose so calculated for replenishment of tissue and storage iron. In the case of iron dextrin with its lower utilization level and of iron sorbitol, a considerable proportion of which is lost in the urine, such dosage requires to be increased by about 50%. This does not, however, make allowance for the patient's weight and requires to be adjusted for unduly heavy or light patients. Each manufacturer issues information on this point with his product and this should be consulted in cases of doubt.

Response to Iron Therapy

For reasons which have been given, the response to oral iron varies from patient to patient. Between 20 and 60 mg. of iron will usually be absorbed daily and red cell production will increase considerably. A reticulocytosis will occur in 5 to 10 days, its degree depending on the initial severity of the anæmia, and the hæmoglobin concentration, after a lag of a few days, will rise at the rate of 0·1–0·25 g./100 ml. per day until it reaches near normal levels. If a response does not occur in 1 month therapy should cease and a cause for the failure sought. Scott and Govan (1949) found that

approximately 14% of their patients showed little or no response in the first month but improved rapidly thereafter. Certainly an automatic change to parenteral iron without seeking a cause for the failure of oral iron, is to be deplored.

The following are the more usual causes of failure to respond to oral iron:

1. *Incorrect Diagnosis*, i.e. the anæmia is not due to iron deficiency or there is no anæmia.
2. *Inhibition of Response by Complicating Disease*, e.g. infection.
3. *Concurrent Blood Loss in Excess of Bone Marrow Activity*, e.g. peptic ulcer, hæmorrhoids, ankylostomiasis, bilharziasis.
4. *Patient Fails to Take Iron.* Every obstetrician has experience of patients who failed to respond to oral iron as out-patients, but responded satisfactorily as in-patients.
5. *Defective Absorption of Iron.* This is uncommon in the absence of clinical intolerance. It occurs in the malabsorption syndromes.
6. *Hæmodilution of Pregnancy.* This, particularly in the later months of pregnancy, may mask the patient's response to iron in terms of a rise in hæmoglobin concentration. Observation of a rise in mean corpuscular hæmoglobin concentration and of the disappearance of anisocytosis and hypochromasia will help to avoid this pitfall. If hæmodilution is mistakenly diagnosed as anæmia iron therapy will elicit no response and, as has been pointed out, the administration of parenteral iron in such cases is accompanied by a high incidence of reactions.

It may be considered that parenteral iron should be used. The indications for change to parenteral iron are:

1. Intolerance to a *variety* of oral iron preparations.
2. Gastrointestinal disease.
3. Creation of iron stores, which is slow in the case of oral iron.
4. Poor absorption of oral iron.
5. Lack of co-operation by the patient. The patient who fails to take the iron prescribed for her may be given her iron parenterally.
6. Urgency. Cases first seen late in pregnancy with severe anæmia may be given parenteral iron as a somewhat more rapid response may be obtained than to oral iron.

As parenteral iron is, to a considerable extent, directly available to the marrow without requiring to pass through the body stores,

the reticulocytosis to be expected is generally greater and earlier than that following oral iron. Scott (1956) has shown that with intramuscular iron the best response is obtained during the first two weeks of treatment, dropping sharply thereafter. A slightly more rapid response is to be expected to intravenous than to intramuscular iron. With intramuscular iron Scott obtained an average increase in hæmoglobin concentration of 0·3 g./100 ml. for every 100 mg. of iron injected. A few cases do not respond to parenteral iron for 1–3 weeks. Scott suggests that this delay is more apparent than real, and accounted for by an initial increase in plasma volume. It is possible, however, that in this case and that of oral iron therapy the delay is due to the preferential transfer of the iron administered, to the iron-deficient fœtus (Callender, 1962).

It is not to be expected that a patient who would respond satisfactorily to oral iron will respond very much better to parenteral iron, and parenteral iron should not be used, if possible, without first trying oral iron.

There remains the question of the level of hæmoglobin which may be considered to be reasonably safe at term, and above which transfusion need not be resorted to. Scott (1962b) states that she aims at a hæmoglobin concentration of above 9 g./100 ml. (62 %). Above this figure the risks of the anæmia are less than those of transfusion.

The Carcinogenic Properties of Intramuscular Iron

Iron dextran was first put on the market in 1954. Three years later Richmond (1957) reported the induction of sarcoma in rats with this preparation. He found that weekly injections of iron dextran over a period of 11 to 16 months caused the development of sarcomata at the site of injection, and that these tumours could be transplanted into further rats. Two years later he published a further paper (Richmond, 1959) verifying and extending his previous work. Weight for weight the dosage used was 200 to 300 times that used in man. He attracted attention to other associations between malignant tumours and iron such as the occurrence of lung cancer in mice inhaling ferric oxide, the high incidence of lung cancer among iron ore miners and the frequency of cancer of the liver in hæmochromatosis.

Shortly after this, Haddow (1959) reported similar results in mice, and that he had observed some tumours at a distance from the injection site, in the liver and lungs. Following a further paper on the subject (Haddow and Horning, 1960) there appeared an

Editorial (1960) in the *British Medical Journal* attracting attention to these reports and stating that, until more was known about the carcinogenic properties of iron dextran, its use in man should be abandoned. This resulted in considerable discussion in the Journal and iron dextran temporarily ceased to be advertized. In the United States its use was apparently discontinued completely.

Golberg (1960) now reported that if doses were reduced to the equivalent of 50 times the clinical dose in man on a weight for weight basis, the incidence of sarcomata fell to levels comparable with those obtained by the injection of accepted innocuous substances such as glucose and fructose. At this point it is relevant to point out that rats and mice are particularly liable, on occasion, to develop local sarcomata at the site of injection of a variety of substances which do not cause malignancy in other animals. Such results are uncommon and bear little if any relationship to the frequently occurring sarcoma induced by large doses of iron dextran. Golberg also pointed out that the local necrotic and inflammatory changes following massive injections do not follow clinical dosage in man and that, in his opinion, these are important factors in determining the onset of malignancy. In addition, Pederson (1960) analysed previous reports and concluded that the relationship between body weight and the dose of iron dextran rather than merely the dose itself was the important factor in determining the onset and frequency of sarcomata. He also pointed out that some iron preparations do not appear to be carcinogenic and that iron dextran is not the only iron preparation with carcinogenic properties when given parenterally.

In the meantime iron dextrin and iron sorbitol became available and observations were extended to these compounds. Andersson and Lundin (1961), using comparatively smaller dosage because of the greater toxicity of iron sorbitol, were able to obtain only one tumour, which they report as having the characteristics of a fibroma, in 35 rats given iron sorbitol, while obtaining a high yield of sarcomata with iron dextrin and iron dextran. Using still smaller doses, but still 40 times the clinical dosage in man on a weight for weight basis, Fielding (1962) obtained a small yield of sarcomata in mice with iron dextrin and iron dextran, and none with iron sorbitol. In the meantime, on 18th December 1961, iron dextran became available again in the United States, but with a label attracting attention to its carcinogenic properties.

The apparent absence of carcinogenicity on the part of iron sorbitol appears to be related to its low molecular weight and to the

fact that it is absorbed into the bloodstream rather than into lymphatics. Because of this absorption is rapid and complete and there is little local histiocytic response. Iron dextrin and iron dextran have molecular weights approximately 20 times that of iron sorbitol. They are absorbed much more slowly from muscle and mainly by lymphatics. After a number of injections in experimental animals they cause regional lymphadenitis and œdema. This delays absorption still further, tissue damage occurs, there is a marked histiocytic reaction and sarcoma follows.

Meanwhile Baker *et al.* (1961) showed that the reaction to small doses or a single large dose of iron dextran soon resolved, whereas that to a series of large doses was irreversible and followed by malignancy. They stressed that these reactions and the development of malignancy were clearly dependent on the relationship between the dose and the bulk of the tissue injected, and not on the absolute size of the dose. This work and the observation that as the dose of iron dextran is reduced the incidence of sarcomata in experimental animals falls considerably, persuaded many workers that iron dextran is safe to use in man in clinical dosage (Editorial, 1961).

Meanwhile three reports have appeared asserting an association between iron dextran and malignancy in man. In the first (Crowley and Still, 1960) a metastasis is reported of an epidermoid carcinoma of cervix at the site of injections of iron dextran. However, metastatic deposits at the site of any injection are by no means unknown, and this does not reflect any carcinogenic property on the part of the injected substance. In the second (Robinson *et al.*, 1960) an undifferentiated sarcoma occurred at the site of injections of iron dextran 4 years previously. However, a minority of pathologists did not consider the lesion to be malignant and it now appears that there is some doubt as to whether the iron dextran was in fact administered into the site stated. In the third (De Jongh, 1960) a patient was given a series of intravenous injections of iron, apparently iron dextran although this is not stated definitely. Some of the iron escaped into the adjacent tissues. A sarcoma, about which no details are given, developed in the left antecubital area in relation to this iron. No further details are given, of time interval or anything else which would help to assess the importance of this as evidence of the carcinogenicity of iron dextran in man, although the site is extremely suggestive.

It is impossible as yet to give a final decision on this question. Iron sorbitol appears to be safe in this connection. In clinical dosage and administered with proper precautions, iron dextrin

and iron dextran probably carry a very small risk of producing malignancy in man, if they carry any at all. Haddow and his colleagues (1964) point out that in all of the experimental animals in which sarcoma has been induced the incubation period has been about one-quarter to one-third of the animal's normal life span. In man this would mean that tumours would not appear for about 15 or 20 years. Iron dextran was introduced in 1954. It remains for the individual practitioner to make his own decision. Iron dextran is an extremely valuable preparation, with little toxicity in other respects, and its use has prevented many transfusions, procedures not without very significant risks.

Megaloblastic Anæmia of Pregnancy

By the term *megaloblastic anæmia* is understood an anæmia in which there is a derangement in red cell maturation with the production in the bone marrow of abnormal precursors known as megaloblasts, and the release into the blood of large erythrocytes known as macrocytes. Not all macrocytic anæmias, however, are megaloblastic. This applies particularly to anæmias accompanied by reticulocytosis, for reticulocytes are larger than mature erythrocytes. In pregnancy true megaloblastic anæmia is not at all rare.

Folic Acid Metabolism

Before discussing the ætiology of megaloblastic anæmia of pregnancy, it is necessary to summarize what is known of the place of folic acid in nucleic acid metabolism. Fig. 12, taken from the work of Baldwin and Dalessio (1961) and Herbert and Zalusky (1962), presents the relative details in simplified form.

Desoxyribonucleic acid (DNA) is present in the chromosome material of nuclei. Cellular division results in a doubling of chromosome material and therefore requires increased synthesis of DNA. This results in an increased demand for both vitamin B_{12} and folinic acid. Ribonucleic acid (RNA) is present in cytoplasm. In neural tissue, with its very low cell turnover, the content of RNA is particularly high. Vitamin B_{12} deficiency, but not folinic acid deficiency, causes a deficiency in RNA resulting in degeneration of neural tissue (subacute combined degeneration). This degeneration is not prevented by the administration of folinic (or folic) acid. In fact, by diverting what little vitamin B_{12} there is available, to DNA synthesis, the administration of folinic (or folic) acid to cases of Addisonian pernicious anæmia causes a fall in serum vitamin B_{12},
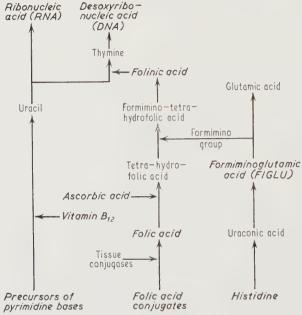
Fig. 12. The metabolism of folic acid and its place in nucleic acid metabolism.

reverts the megaloblastic bone marrow picture to normoblastic and remits the anæmia, while precipitating subacute combined degeneration.

Folic acid conjugates are absorbed from food and converted to folic acid by tissue conjugases. Ascorbic acid and other reducing substances reduce folic acid to tetra-hydro-folic acid. This accepts a formimino group from the catabolism of FIGLU to glutamic acid, to form formimino-tetra-hydro-folic acid. The conversion of the formimino group to a formyl group leads to the formation of folinic acid, which is the active coenzyme in DNA synthesis.

It is apparent from Fig. 12 that a deficiency of tetra-hydro-folic acid, whether this be due to deficient intake of folic acid or its conjugates, or to a block in their metabolism to tetra-hydro-folic acid, such as would occur in ascorbic acid deficiency, will block the metabolism of histidine at the FIGLU stage, since the acceptor of the formimino group ceases to be available. This is the rationale behind the FIGLU test.

In addition to the vitamin B_{12} and folic acid available from the diet, there is some production of these substances by bacteria in the alimentary canal. In the case of vitamin B_{12}, however, this is over-shadowed by the uptake by other such bacteria and Foy and his colleagues (Foy and Kondi, 1953; Foy *et al.*, 1955) were able to show that in tropical megaloblastic anæmia of pregnancy, those cases which respond to vitamin B_{12} will also respond to penicillin.

Ætiology

The discovery of folic acid arose out of the early work of Wills who showed that most cases of megaloblastic anæmia of pregnancy will respond to crude liver extracts and yeast extracts but not to refined liver extracts. It is now known that the former contain folic acid while the latter does not, and "Wills' factor" was undoubtedly folic acid.

The requirement of folic acid by the normal adult is of the order of 50 μg. per day (Herbert, 1964). Spies (1949) has estimated that in pregnancy this rises to 3–5 mg. per day, a sixty to one hundred-fold increase. A number of factors arise in pregnancy which increase the demands for folic acid. These are, first, the increase in maternal tissues and in maternal red cell volume. As has been shown, the latter can be considerable and is accompanied by an increase in bone marrow erythropoietic activity. The demands by the developing products of conception require to be met, and it has been shown that the cord blood levels of vitamin B_{12}, folic acid and particularly folinic acid are usually greater and often much greater than the mother's (Baker *et al.*, 1958; Rachmilewitz and Izak, 1960). It is not unexpected therefore that the greatest incidence of megalo-blastic anæmia coincides with the greatest fœtal demands, the maximum increase in maternal tissues, the greatest increase in maternal red cell volume and, as will be seen, the highest clearance rate of intravenously injected folic acid. Nor is it surprising that megaloblastic anæmia is much commoner in twin than in single pregnancies.

Certain complications of pregnancy increase the demands for folic acid, divert its use from erythropoiesis or depress its intake or absorption. These are of importance in the causation of megalo-blastic anæmia. Thus abnormalities of appetite and nausea and vomiting which often accompany pregnancy may result in a deficient intake of folic acid. The main sources of folic acid in the diet are dark green vegetables, cauliflower, liver, kidney and brewer's yeast and the non-availability of the first two of these in fresh form

coincides with the seasonal incidence of megaloblastic anæmia in winter and early spring noted by a number of workers. Infections reduce the life span of red cells so increasing the demand for folic acid, and by increasing tissue metabolism divert it from the metabolism of red cells. Hæmorrhage such as occurs with peptic ulcer, hæmorrhoids, ankylostomiasis and bilharziasis results in increased erythro- and leucopoiesis with increased demands for folic acid and vitamin B_{12}. Hæmolytic diseases act similarly. Chanarin, Dacie and Mollin (1959) report an association between megaloblastic anæmia and a variety of hæmolytic anæmias in non-pregnant subjects. As will be seen, the association in pregnancy is much closer.

There can be little doubt that the greater incidence of megaloblastic anæmia in the tropics and its generally greater severity is caused not only by dietary deficiency but also by the increased demands for folic acid and vitamin B_{12} by such hæmorrhagic conditions as ankylostomiasis and bilharziasis, and such hæmolytic conditions as chronic malaria and the hæmoglobinopathies.

Malabsorption of folic acid may be a factor, and has been observed in about 30% of their cases of megaloblastic anæmia by Giles and Burton (1960) and by Chanarin, MacGibbon et al. (1959). This has not, however, been everyone's experience.

The association between ascorbic acid and folic acid in food is close and a deficient intake of one is likely to be accompanied by a deficiency of the other. As can be seen from Fig. 12, ascorbic acid deficiency will block the conversion of folic acid to the active coenzyme folinic acid, and may contribute to the onset of megaloblastic anæmia. It is of interest to observe at this point that Hoch and Marrack (1948) found that the plasma ascorbic acid level is generally low in pregnancy, and that many workers have found the plasma levels of folic (not *folinic*) acid to be high, normal or only slightly low in many cases of megaloblastic anæmia of pregnancy. Certainly the folic acid level is not usually as low as that which occurs in other folic acid deficiency megaloblastic anæmias (Witts, 1962). Scott's (1957) dramatic cures with short courses of folinic acid in rather small doses may be pertinent in this connection.

Nevertheless, dietary deficiency of folic acid is the most important ætiological factor, as Giles and Shuttleworth showed when they found that 42% of their cases of megaloblastic anæmia of pregnancy were on an inadequate diet.

Many reports have now appeared on serum folic acid levels and the response to intravenous and oral folic acid in pregnancy with and without megaloblastic anæmia. Almost invariably the micro-

organisms used in the microbiological assay have been *L. casei* or *Strep. fæcalis*, and there is some variation in the findings of different workers. Roughly speaking the following are estimated by the three assay techniques most used:

1. *L. casei* estimates conjugated folic acid, free folic acid and folinic acid.
2. *Strep. fæcalis* estimates free folic acid and folinic acid.
3. *L. citrovorum* (*P. cerevisiæ*) estimates folinic acid.

There is however some slight overlap.

Most workers have found that serum folic acid levels (*L. casei* factor) fall progressively during pregnancy (Witts, 1962; Ball and Giles, 1964). This fall is more marked in twin pregnancies than in single pregnancies, and most marked in cases with megaloblastic anæmia. This statement, however, refers to the average results obtained in groups of subjects. In individual patients the results vary widely and there is considerable overlap between normal results and those in pregnancy, twin pregnancy and megaloblastic anæmia. Witts (1962) points out that 16% of cases with megaloblastic anæmia have normal serum folic acid levels. On the other hand, Ball and Giles (1964) showed that serum "labile folic acid", which is closely related to folinic acid, was low in all of their cases of megaloblastic anæmia of pregnancy and in only 1 out of 35 cases with normoblastic bone marrows.

The interpretation of individual serum folic (as opposed to folinic) acid levels is therefore doubtful and as Solomons *et al.* (1962) point out, this even applies to folic acid levels in groups of patients. These workers observed the falling serum folic acid (*L. casei* factor) level in the course of pregnancy and noted that it was parallelled by an increasing incidence of anæmia, in a group of patients. However, they found no correlation between the presence or severity of anæmia and the serum folic acid levels in the individual cases. Their lowest serum folic acid levels occurred in non-anæmic subjects and they did not find any hæmatological differences in anæmic patients with high and low serum folic acid levels respectively. In addition some workers, for example Baker *et al.* (1957) have found serum folic acid to rise in pregnancy. It is apparent that studies based on *L. casei* activity, while giving information of value in research, can merely be confusing when applied to the individual case.

Much interest has been aroused by the work of Chanarin, Mac-Gibbon *et al.* (1959) on the clearance of intravenous folic acid in

Table 33

FOLIC ACID CLEARANCE IN PREGNANCY

Subjects	Percentage with Rapid Folic Acid Clearance
Normal, non-pregnant	Nil
Normal pregnant, 12 weeks	8
Normal pregnant, 21–24 weeks	33
Normal pregnant, 37–40 weeks	68
Normal twin pregnancy	100
Megaloblastic anæmia of pregnancy	100

pregnancy. Their results are summarized in Table 33. They used *Strep. fæcalis* for their assay; in other words they estimated free folic acid, and folinic acid. They interpret these results as meaning that there is a progressive tissue deficiency of folic acid in normal pregnancy in many cases, and that this is always so in twin pregnancies and in megaloblastic anæmia. This interpretation, however, depends on the necessity for folic acid administered in this way to go into the body stores before becoming available for DNA synthesis, and this has never been demonstrated. It is at least as likely that this is not so, and therefore that, at least in normal pregnancy and twin pregnancy without megaloblastic anæmia, its rapid clearance merely reflects increased erythropoiesis and the other metabolic processes which require folinic acid. In megaloblastic anæmia the interpretation is presumably more acceptable, although here the diversion of part of the folic acid into some abnormal metabolic pathway (as has been suggested) is possible. In this connection the considerable overlap in individual results which was observed remains a disturbing feature in their interpretation, particularly in the individual case.

With regard to the serum vitamin B_{12}, this has been shown on many occasions to fall steadily in the course of pregnancy. This does not, however, necessarily indicate a true deficiency, and the levels rise to normal in the puerperium without therapy. In the tropics, however, vitamin B_{12} deficiency is not an uncommon cause of megaloblastic anæmia in pregnant women. Apart from the causes which have been suggested, such as dietary deficiency, hæmorrhage and hæmolysis, Herbert (1959) has pointed out that a diet high in phytates blocks the calcium bonds responsible for the uptake of vitamin B_{12} by the cells of the intestinal mucosa.

While the vast majority of cases of megaloblastic anæmia in pregnancy are of the type discussed, this is not necessarily always so. Thus Girdwood (1956) lists the following megaloblastic anæmias as being possible in pregnancy:

1. Nutritional megaloblastic anæmia, complicated and aggravated by pregnancy. Many tropical cases belong to this group, as well as a few in temperate regions.
2. Megaloblastic anæmia of pregnancy. This is the type occurring typically in temperate regions.
3. Addisonian pernicious anæmia in a pregnant woman.
4. Addisonian pernicious anæmia complicated by megaloblastic anæmia of pregnancy.
5. Megaloblastic anæmia of the malabsorption syndromes, complicated and possibly aggravated by pregnancy.

Incidence. It was once thought that megaloblastic anæmia of pregnancy is rare in Western countries. In recent years, however, as criteria for the diagnosis of the condition have changed, the frequency with which the anæmia is diagnosed has increased until it is now reported as occurring in up to about 4% of all pregnancies in this country and Eire (Giles and Shuttleworth, 1958; Mackenzie and Abbott, 1960; Hourihane *et al.*, 1960). In many more cases evidence of folic acid deficiency without megaloblastic change can readily be obtained.

It is commoner in twin than in single pregnancies. Thus Lillie (1962) found it to occur in 17% of twin pregnancies not on prophylactic folic acid. Its frequency tends to be higher in Winter and Spring, but reports on this point vary and some observers have not found this to be so. Its incidence in the tropics is generally much higher than that in Western countries, and it appears to be very infrequent in the United States (Solomons *et al.*, 1962).

Clinical Findings. The condition is generally diagnosed in the third trimester or the puerperium, but as interest in this form of anæmia increases, so does the frequency with which it is diagnosed earlier in pregnancy. It is usually of gradual onset but sometimes appears to develop rapidly, particularly in the puerperium. Patients are usually, but not always, multiparous and in the middle or later years of reproductive life. Its association with twin pregnancies has been mentioned. It may be accompanied or precipitated by more obvious causes of ill-health such as sepsis, toxæmia of pregnancy and hæmorrhage. Coyle and Geoghegan (1962) report that of 77 cases of severe accidental hæmorrhage, 35 had a megaloblastic bone

marrow. A minority of the cases are malnourished and the majority come from the poorer classes. The association between diet and megaloblastic anæmia of pregnancy is stressed by Giles and Shuttleworth (1958) who report a poor diet in 42% of their cases of megaloblastic anæmia as against 4% of their healthy patients.

Gastrointestinal complaints tend to be prominent and, in severe cases, splenomegaly and less commonly hepatomegaly may be present. Pyrexia is common and often, but not always, due to sepsis. Glossitis, œdema and albuminuria are frequently found in severer cases and purpura and retinal hæmorrhages are occasionally seen. Apart from these features the symptoms are those of any other anæmia.

Diagnosis. Typically the findings are of a macrocytic hyperchromic anæmia without reticulocytosis. The cells in the peripheral blood are large, fully hæmoglobinized and tend to be oval. There may be considerable anisocytosis and poikylocytosis (Fig. 13) and macropolycytes may be found. Generally the changes in the blood picture are not as marked as in Addisonian pernicious anæmia and may
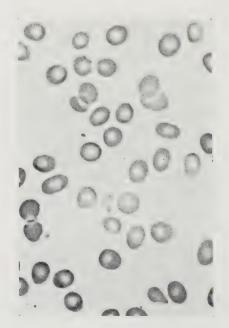
Fig. 13. Blood film of megaloblastic anæmia of pregnancy.

be masked by concurrent iron-deficiency anæmia. In such cases iron therapy may unmask the megaloblastic picture.

It is unusual to find many megaloblasts in films of the peripheral blood but in many cases they can be demonstrated in films of the leucocyte layer after centrifugation.

If megaloblasts are not found in the peripheral blood, bone marrow examination should be carried out. As compared with the normoblast, the megaloblast is larger and shows hæmoglobinization of its cytoplasm in advance of its nuclear development and certain abnormalities of nuclear structure (Figs. 14–15). Typical megaloblasts may be scanty or absent and the diagnosis may depend on the demonstration of transitional megaloblasts, cells intermediate in morphology between normoblasts and megaloblasts, Layrisse (1960) and Rachmilewitz and Izak (1960) state that this is so when there is concurrent iron deficiency. Sometimes the diagnosis may be made only by demonstrating giant metamyelocytes, Howell-Jolly bodies in more than 1 % of polychromatophilic and orthochromatic normoblasts (Dawson, 1962) or large hypersegmented polymorphs (macropolycytes). Extending the diagnostic criteria in this way has un-
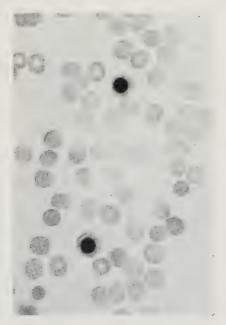
Fig. 14. Normoblastic bone marrow.
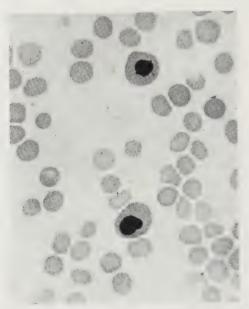
Fig. 15. Megaloblastic bone marrow.

doubtedly contributed greatly to the increased frequency with which the diagnosis of megaloblastic anæmia of pregnancy is now made. As megaloblasts are not considered to be essential now, it would seem that consideration will need to be given to a new name for this anæmia!

Estimations of vitamin B_{12} and folic acid can only be made in larger centres and the results are sometimes equivocal. They will be discussed later.

When it was discovered that increased urinary excretion of formiminoglutamic acid (FIGLU), particularly after histidine loading, occurs in other folic acid deficiency megaloblastic anæmias it was applied to the diagnosis of megaloblastic anæmia in pregnancy. Thus Hibbard (1962) claimed that this test is much more accurate than bone marrow examination in determining which cases will respond to folic acid, apparently having an accuracy of 100% in her hands. This has not, unfortunately, been the experience of other workers. Chanarin et al. (1963) found no increase in FIGLU excretion in 50% of their cases of megaloblastic anæmia of pregnancy. Husain et al. (1963) found no differences between the hæmo-

globin concentrations of their FIGLU positive and FIGLU negative cases. Some patients who were FIGLU positive at the 28th week of their pregnancy became FIGLU negative later without folic acid therapy. Some patients swung to and fro between positive and negative results. Even more disturbing is the observation by Berry *et al.* (1963) that while the frequency of positive FIGLU tests falls from 36% of all pregnancies at or before the 16th week, steadily to 5% at the 35th week, the incidence of megaloblastic anæmia behaves in an opposite manner. It should be pointed out also that FIGLU positive tests occur not only in folic acid deficiency but also, for example, in some cases of vitamin B_{12} deficiency.

The reasons for the failure of the FIGLU test in pregnancy are the lowered renal threshold for histidine which is often present at this time, so that much of the loading dose disappears into the urine. The growth of the fœtus requires large quantities of histidine for protein synthesis, so that some of the dose is diverted away from the formation of FIGLU. Finally, in pregnancy oral histidine is absorbed slowly, so that the oral loading by histidine is interfered with.

It is advisable that all patients with megaloblastic anæmia in pregnancy be examined for histamine-fast achlorhydria. This, also known as absolute achlorhydria, is present when the patient fails to secrete hydrochloric acid even when parenteral histamine is administered. There is no association between megaloblastic anæmia of pregnancy and absolute achlorhydria, and such patients should be considered as having Addisonian pernicious anæmia also, until shown to be otherwise.

Treatment

While it is true that cases of mixed ætiology occur even in Western countries, and that some cases respond to vitamin B_{12}, the treatment of megaloblastic anæmia of pregnancy here is folic acid, in a dosage of 20 mg. daily by mouth unless folinic acid is available. Ascorbic acid should also be given, and treatment should be continued until the blood picture has been normal for 1 month in the puerperium and may then stop. Recurrence in subsequent pregnancies is a definite possibility. The rapid red cell formation which follows treatment may unmask a concurrent iron deficiency, and it is advisable to give iron also, except when there is an underlying hæmolytic condition. If time is short treatment may begin with 30 mg. of folic acid intramuscularly daily for 3 days, or with 90 mg. intravenously in 250 ml. of physiological saline, and be continued

with oral therapy. Initial blood transfusion may be required if the case is seen very late in pregnancy, or with a very low hæmoglobin concentration.

If there is no response to folic acid a cause such as occult hæmorrhage or hæmolysis may be present, and should be searched for. If this fails, recourse must be had to treatment by trial and error. In such cases combinations of folic acid, ascorbic acid, vitamin B_{12} and high protein intake may be tried. Sometimes vitamin B_{12} alone is effective.

Folic acid will also be effective in the megaloblastic anæmia of the malabsorption syndromes, although in these cases parenteral administration, at least initially, may be required, and in some cases of tropical nutritional megaloblastic anæmia.

It is the case of megaloblastic anæmia in a pregnant woman with histamine-fast achlorhydria which presents the greatest problem. She should be treated as if she had both Addisonian pernicious anæmia and megaloblastic anæmia of pregnancy. In other words, she should be given both folic acid and *parenteral* vitamin B_{12}, unless facilities are available for more complete diagnosis. Since this normally requires radioactive isotope studies, it is probably best left to the puerperium. Both folic acid and vitamin B_{12} may be discontinued when the blood picture has been normal for 1 month in the puerperium. If hydrochloric acid secretion returns, no further difficulty need be expected. If not, the patient should be followed up for at least 2 years, unless arrangements can be made for special investigations, and at the first evidence of relapse, treated as a case of Addisonian pernicious anæmia.

Addisonian pernicious anæmia is rare in pregnancy and in most cases will have been diagnosed before conception. It is said that these women tend to be infertile. A number of cases, however, have now been reported and, in this connection, the observations of Adams (1958) are of interest. He points out that cases on parenteral vitamin B_{12} do very well, but that those on oral vitamin B_{12} with intrinsic factor tend to relapse and must be changed over to parenteral therapy.

For the prevention of megaloblastic anæmia of pregnancy careful supervision, the maintenance of general health, the immediate treatment of complications and attention to diet and nutrition will do much to reduce the incidence of the disease. The administration of small doses of folic acid (3 mg. per day) with or without vitamin B_{12} appears to reduce the incidence to zero (Giles and Burton, 1960; Lowenstein *et al.*, 1955). Lillie (1962) reports success in

preventing the condition in twin pregnancies with a daily supplement of 5 mg. of folic acid. The risk of inducing subacute combined degeneration in an unsuspected case of Addisonian pernicious anæmia is admittedly slight but does exist. It is not true to say that small doses of folic are safe in this connection, for many such cases apart from pregnancy have now been reported, and no doubt, as the practice of giving prophylactic folic acid spreads, the first case in pregnancy will eventually be reported.

Effects of Anæmia in Pregnancy

Most of the recent observations have been made on the effects of megaloblastic anæmia. As this condition is diagnosed earlier and more frequently, so the prevalence and nature of its effects become clearer. Nevertheless, experiences vary and one must be tentative in accepting any single worker's observations. Nor is it always possible to say which is cause and which effect.

Anæmias of any severity, irrespective of their ætiology, are associated with an increased incidence of infections, stillbirths and neonatal deaths, miscarriages, premature labour and postpartum hæmorrhage. Megaloblastic anæmia appears to be specifically associated with an increased incidence of hypertension and albuminuria, undersize infants, hydramnios and antepartum hæmorrhage. Some workers deny that the picture of "toxæmia" of pregnancy is associated with megaloblastic anæmia, and find it to be commoner in non-anæmic subjects.

It may, however, be stated unequivocally that the prevention of anæmia improves the well-being of both the mother and her infant, and that severe anæmia is accompanied by a high maternal and, particularly, infant death rate.

Hæmolytic Anæmias in Pregnancy

Until recent years association between hæmolytic anæmias and pregnancy was rare in this country and attracted little attention. However, with the increasing number of immigrants from Africa, the West Indies and the Indian subcontinent, and the development of techniques for the identification of the abnormal hæmoglobins, many cases have been studied and much interest has been aroused in this problem. Attention will be confined here to the abnormal hæmoglobin designated S, and its association with other hæmoglobinopathies in pregnant women, since this has attracted most attention.

There are three normal hæmoglobins, designated by the letters A, A_2 and F. Hæmoglobin A is that which occurs as the normal hæmoglobin of adults. Hæmoglobin A_2 is present in normal adult blood as not more than 3% of the total hæmoglobin. Hæmoglobin F is that which occurs as about $50–100\%$ of a new-born infant's hæmoglobin, disappearing during the first year of its life. It is normally present, in low concentration, in the blood of pregnant women in virtue of the presence of fœtal cells within their circulation.

In the conditions known as *thalassæmia* there is a genetic defect in hæmoglobin A synthesis. Thalassæmia occurs in two clinical forms, a major homozygous form in which the abnormal gene is inherited from both parents and the clinical features are severe, and a minor heterozygous form in which the abnormal gene is inherited from one parent only and the clinical features are mild. The deficiency in hæmoglobin A synthesis is compensated for by an increased synthesis of hæmoglobin A_2 (in thalassæmia major and minor), and a persistence of Hæmoglobin F (in thalassæmia major). It will be noticed that the hæmoglobins which occur in thalassæmia are "normal". Hæmoglobin F resists conversion to alkaline hæmatin (alkali denaturation), and this property can be used to demonstrate its presence and estimate its concentration.

The abnormal hæmoglobins have been designated by other letters such as C, D and S, although one or two have been given names ("Barts", "Lepore", Norfolk"). The synthesis of the various hæmoglobins is under the influence of genes which are alleles of that which determines the synthesis of hæmoglobin A. In other words, one such gene only can be transmitted by a parent to his or her offspring, and the resulting genetic pattern will be homozygous or heterozygous depending on whether the parents transmit identical or differing genes. The genes which determine the presence of thalassæmia are not alleles of the gene for hæmoglobin A and are transmitted independently. Of the abnormal hæmoglobins, that designated S is peculiar in that it is comparatively insoluble in the reduced state, precipitating out as crystals which distort the cells into forms known as "sickle cells". The heterozygous presence of an abnormal gene with the normal gene produces a *trait* which is symptomless under normal conditions. Thus sickle cell trait has the genetic pattern AS, and hæmoglobins A and S, and hæmoglobin C trait has the genetic pattern AC, and hæmoglobins A and C. The homozygous presence of an abnormal gene, or the heterozygous presence of two abnormal genes produces a *disease*, such as sickle-cell anæmia (genetic pattern SS) and sickle-cell hæmoblobin C

disease (genetic pattern SC). In the homozygous, and sometimes in the heterozygous hæmoglobin diseases, hæmoglobin F usually persists throughout life. Thus the hæmoglobins present in sickle-cell anæmia and in hæmoglobin C disease are hæmoglobins S + F and C + F respectively. It will be realized that these are also the hæmoglobin patterns of sickle-cell thalassæmia and hæmoglobin C thalassæmia respectively. It is therefore not always possible to diagnose the disease from the nature of the hæmoglobins present. This requires study of the whole family.

Much is now known of the world distribution of these abnormal genes. For details the reader is referred to the work of Lehmann (1960) and Harris (1963). The gene for thalassæmia occurs in a broad band from Spain across the northern and southern shores of the Mediterranean, through the Eastern Mediterranean and Arabian countries and the Indian sub-continent to South-East Asia. The gene for hæmoglobin C occurs with a frequency of about 20% in northern Ghana and the adjacent territories and diminishes in frequency into the surrounding country. The gene for hæmoglobin S occurs in a wide band across equatorial and tropical Africa and appears to have originated in East Africa. It also occurs in parts of the Mediterranean and Arabian countries and Southern India. Overlap is therefore considerable and the heterozygous hæmoglobin diseases are frequently met with.

Before discussing the hæmoglobin diseases in detail two points may be made at once. These diseases are associated with a shortened red cell life span and therefore with increased red cell production and demands for folic acid. Folic acid deficiency (and probably vitamin B_{12} deficiency) are therefore particularly liable to occur in pregnant women with these conditions. The routine administration of folic acid under these circumstances is strongly indicated and will reduce the maternal death rate materially. They are hæmolytic diseases and are normally accompanied by high serum and store iron levels. These patients should not therefore be given routine prophylactic iron and should certainly not be given parenteral iron without proof of concurrent iron deficiency.

When looked for, the incidence of abnormal hæmoglobins and thalassæmia, generally expressing themselves as traits, is high. Thus Dixon (1962) reports a proven incidence of 38·5% and a probable further incidence of 24·5% among coloured pregnant women with hæmoglobin levels below 11·1 g./100 ml.

Transfusion in Sickle-cell Diseases. In both hæmoglobin S and SC disease, severe anæmia and sudden falls in hæmoglobin concen-

tration are frequently met with, particularly if the patient is not on prophylactic folic acid. The normal hæmoglobin concentration in sickle-cell disease is around 8 g./100 ml. The patient is well adjusted to this and does not need transfusion at this hæmoglobin level. The comparative figure for sickle-cell hæmoglobin C disease is about 12 g./100 ml. When transfusion becomes necessary, the use of ordinary whole blood transfusions is to be avoided, for these are accompanied by a high incidence of sickling crises, aplastic crises, congestive cardiac failure and maternal death. Packed cells should be given, slowly and a little at a time, or, in the most severe cases, exchange transfusion should be carried out (Fullerton and Watson-Williams, 1962). Blood should also be available during labour in case of ante- or postpartum hæmorrhage.

Sickling Crises. A feature of the presence of hæmoglobin S is the occurrence of clinical crises due to sludging of erythrocytes within capillaries. Such crises are common in sickle-cell disease and, in pregnancy, in sickle-cell hæmoglobin C disease. They are rare in sickle-cell trait and the other sickle-cell diseases and are then associated with severe anoxia. Sludging is caused by the distortion of erythrocytes occasioned by the crystallization of reduced hæmoglobin S, and is contributed to, apart from anoxia, by stasis, local acidosis and transfusion. Fibrin is deposited around the sludged cells so that thrombosis supervenes, and this may extend into the veins. Infarctions of the bone marrow, spleen and other organs may occur and the patient presents with pyrexia, leucocytosis, bone pains and abdominal pains. Pulmonary embolism may occur, either by infarcted bone marrow or by thrombus from veins.

Prevention requires careful obstetric and anæsthetic technique during delivery, to avoid trauma, anoxia and blood loss. Barbiturates, either as sedatives or in anæthesia, are probably best avoided. In full dosage they have some depressant effect on respiration and their use may induce hypoxia. Sodium bicarbonate may be given throughout pregnancy to keep the urine alkaline and maintain the plasma bicarbonate at high levels, and this appears to be beneficial (Apthorp and Lehmann, 1964). Oxygen may be helpful during labour and should be given for at least 24 hours if a general anæsthetic has been administered. For the treatment of crises Apthorp and Lehmann (1964) recommend that 2 ml. of 50% magnesium sulphate be given intravenously every 4 hours until the pain is relieved and treatment be continued with oral 70% magnesium glutamate every 6 hours for a further 5 days. The rationale is that this is vasodilator, decreases sludging and viscosity and delays fibrin deposition. Watson-Williams

(1963) has had success with low molecular weight dextran. They administer 500 ml. of a 10% solution in physiological saline in the first 30 minutes and follow this up with a further 500–800 ml. in the next 8–15 hours. They also recommend the use of heparin. Other workers, however, state that this makes the crises worse. Acetazoleamide may also be tried (Curtis, 1959).

Sickle-cell Trait. With the exception of the occurrence of sickling crises in the presence of severe hypoxia, this condition presents no unusual difficulties in pregnancy.

Sickle-cell Disease. When this condition is diagnosed in a pregnant woman it is advisable, if possible, that she be hospitalized for the remainder of her pregnancy. Such cases are uncommon since the disease is associated with a low fertility rate. A history of anæmia and sickling crises is always obtainable and in many cases the diagnosis has already been made. The typical clinical features, disproportionately long legs, hyperextensile fingers, leg ulcers and cardiomegaly are usually present. As with sickle-cell hæmoglobin C disease, such cases require the optimum of obstetric care. Infections should be treated vigorously and at once and sudden exposure to cold should be avoided. Nevertheless, unlike sickle-cell hæmoglobin C disease, pregnancy does not appear to have any effect on the progress of sickle-cell disease. The effect of the disease on the pregnancy is not, however, by any means benign and the incidence of spontaneous abortions is about 20%, of premature delivery about 30% and of fœtal deaths about 50%. There is no increase in maternal deaths.

Sickle-cell Hæmoglobin C Disease. This disease, milder than sickle-cell disease apart from pregnancy, becomes much more serious when pregnancy occurs. Apart from pregnancy it has little effect on longevity and is not associated with the physical stigmata of sickle-cell disease. There may be a history of hæmolytic and sickling crises, but this is not always so and the disease may not have been diagnosed before pregnancy. Splenomegaly may be present, but not invariably. During pregnancy the frequency and severity of sickling and hæmolytic crises increases, particularly as term approaches. Hæmolytic crises are particularly frequent if malaria or folic acid deficiency are also present. Folic acid should be administered routinely and malaria looked for and treated. In malarial areas, prophylactic antimalarials should be given.

The special precautions are those previously described. In unbooked cases, a maternal death rate of over 20% is to be expected on account of anæmia, pulmonary embolism or other complications.

With optimal antenatal care this may be reduced to about 5%
(Fullerton and Watson-Williams, 1962) but still remains significant.
The frequency of spontaneous abortions, premature delivery and
fœtal death is increased but is not as high as in sickle-cell disease.
In neither this nor in sickle-cell disease are premature induction of
labour or Cæsarean section of help. After the pregnancy, sterilization
may be considered in cases of sickle-cell hæmoglobin C disease.

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THE INTERPRETATION OF SEROLOGICAL TESTS
FOR SYPHILIS

It must be made clear at once that there are no serological tests which will differentiate syphilis from the related diseases yaws, pinta and bejel. This has become important in this country in the management of immigrants from areas in which yaws is endemic who present with positive serological tests. The residual signs of yaws which persist into adult life, such as scars on the legs, are not diagnostic. If, as is usually the case, it is impossible to obtain details of the original diagnosis and treatment, these cases should be dealt with as cases of late latent syphilis.

The serological diagnosis of syphilis depends on the demonstration of one or more of three antibodies:

1. *Reagin*. This is the antibody demonstrated in the classical complement fixation and flocculation tests such as the Wassermann and Kahn reactions. The antigen used in these tests, originally prepared from syphilitic liver and later from a variety of tissues including heart muscle, has been shown to be a chemically pure substance, cardiolipin. This substance is combined, in modern tests of this group, with lecithin and cholesterol and is used in the popular Cardiolipin Wassermann Reaction (CWR) and Venereal Diseases Research Laboratory (VDRL) test.

This, the *Treponemal Group Antibody*, is tested for with a protein extract of the Reiter spirochæte in the Reiter Protein Complement Fixation Test (RPCFT).

Specific Antibody. This is tested for in a number of recently developed tests of which the most important are the *Treponema pallidum* immobilization test (TPI) and the fluorescent treponemal antibody test (FTA). The TPI test depends on the immobilization and killing of a live suspension of virulent *T. pallidum* by a positive serum in the presence of complement. The FTA test depends on the fluorescence in ultraviolet light of a dried fixed film of virulent *T. pallidum* exposed to a positive serum from which it absorbs out antibody and then treated with antihuman γ-globulin serum conjugated with fluorescein isothiocyanate.

Of the tests mentioned the TPI is the most sensitive and the CWR and VDRL the least. The sensitivity of the FTA and RPCFT are generally approximately equal and intermediate in degree. The sensitivity of the tests varies with the stage of the disease and whether or not treatment has been given. In primary syphilis tests for reagin will be positive in about 55% of cases and the Reiter and fluorescent antibody tests in about 75%. In secondary syphilis all tests are uniformly positive. In late symptomatic syphilis the sensitivity ranges from 80% in the tests for reagin to about 95% in the fluorescent antibody test. At all stages false negative results with the treponemal immobilization test are rare. Therapy causes the tests for reagin to become negative most rapidly and a persistent positive probably means failure to cure. At the other extreme the TPI test is hardly influenced when treatment is started late in the disease and, on this account, cannot be used as a test of cure.

The earliest to become positive is the fluorescent antibody test, followed shortly by the Reiter test. A few days later, about 4 weeks after infection, reagin tests become positive. Treponemal immobilization is the last to appear.

With regard to specificity, a positive TPI or FTA test always indicates syphilis (or its related diseases). Reports on the specificity of the other tests vary widely, but are about 97% for the Reiter test and rather less than this for reagin tests.

Interpretation

If the clinical evidence is strong and tests for reagin are positive, confirmation by the Reiter protein complement fixation test is all that is needed. The indications for requesting a treponemal immobilization test are:

1. Cases with positive reagin tests in which there is no clinical history or evidence of syphilis and it is suspected that the positive tests are non-specific.
2. Cases in which the routine tests are negative but the clinical picture suggests syphilis. In such cases a positive TPI means syphilis and a negative renders the diagnosis very unlikely.
3. Instances sometimes occur of positive reagin tests with a negative Reiter test. In about 80% of cases these are false positive results and a TPI test should be carried out.

The *Treponema pallidum* immobilization test is expensive, time-consuming, dangerous to the technician and technically difficult. It should not be requested unnecessarily. It is important that penicillin be withheld for at least 14 days before collecting blood for this test, since even minute traces of penicillin interfere. If this is impossible the reference laboratory should be informed so that the serum may be treated with penicillinase.

Biologically False Positive Results

(Moore and Mohr, 1952; Catterall, 1961)

These are positive results obtained with tests for reagin in the absence of syphilis. Usually, but not always, the Reiter test is negative. Tests for specific antibody are, of course, always negative. Such positive results are "false" only in that they do not indicate syphilis. They are not due to technical error. In other words, the result is correct but if syphilis is diagnosed in virtue of the positive result, the interpretation is wrong.

A trace of reagin is present in the serum of normal persons, but this is only rarely demonstrable by the ordinary tests. Generally, however, such positive tests are related to other diseases. Biologically false positive tests may be acute or chronic and are usually, but not always, of low titre.

1. *Acute*. These occur during or within 6 months of a nonsyphilitic illness and are of limited duration. They occur in a wide variety of bacterial, viral, spirochætal, rickettsial and protozoal diseases. They probably occur in all cases of malaria. They occasionally occur in blood donors and in pregnancy itself.

2. *Chronic*. These persist for many months or years, or even for life. They occur in many cases of leprosy and sometimes in the collagen diseases. Prolonged follow-up of apparently healthy cases has shown that a high proportion, particularly of the females, develop serious disabling illness, most commonly disseminated lupus erythematosus, within a few years. Many of these cases give a history of sensitivity to penicillin, and antisyphilitic treatment has no effect on the positive test. A family history of collagen disease may be obtained, and many cases show hypercholesterolæmia. It is said that adrenal cortical hormones render the tests negative while they are being given.

It is apparent that a false positive reagin test is not to be dismissed lightly. If it persists intensive investigation and prolonged follow-up are indicated in an attempt to determine the cause.

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THE AMNION AND CHORION

The Amnion

The amnion is the inner of the two human fœtal membranes and, as such, is in contact with the contents of the amniotic sac, namely the amniotic fluid and the fœtus. The chorionic membrane, which is adjacent to the outer surface of the amniotic membrane, separates the amnion from the decidua of the maternal uterus. The placenta is a chorionic structure and is lined on its inner aspect by the amniotic membrane; this part of the amnion is called the *placental amnion*, whilst the remainder is referred to as the *reflected amnion*. It is considered possible that the placental amnion might perform a specific physiological function, on account of its close relationship to the fœtal vascular network within the placenta. The histological differences between these areas are not great. A third area that directly overlies the internal os of the cervix and covers an area of only one or two square centimetres is known as the *dependent amnion*, and this small section may occupy any part of the amniotic sac in relation to the placenta.

It is now generally accepted that the human amnion is not merely an epithelial lining for the uterine contents, but that it is a complicated tissue constructed histologically of five different layers (Bautzmann and Schroder, 1955; Schmidt, 1956; Petry and Damminger, 1956; Bourne, 1960; Bourne, 1962).

Figure 16 is a semi-diagrammatic illustration of the amnion and chorion. The face of this illustration shows the layers as they are seen when cut in vertical section, whilst the treads of the steps show their appearance in membrane preparations.

The five layers of the amnion, from within outwards, are:

a. The Epithelium. This is normally composed of a single layer of apparently simple non-ciliated cuboidal cells. Recent research has implicated amniotic epithelium in the exchange of fluid and electrolytes that is now known to occur between the amniotic sac and the mother (Hutchinson *et al.*, 1959; Jeffcoate and Scott, 1959; Vosburgh *et al.*, 1948). Does the amnion secrete liquor? Or does it
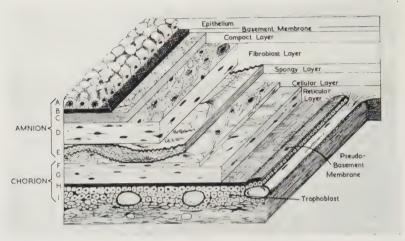
Fig. 16. Section through human amnion and chorion (diagrammatic). Composite diagram to illustrate the appearance of the layers of reflected amnion and chorion.

absorb fluid? Or does it both secrete and absorb? To these questions there is, as yet, no satisfactory answer.

b. The Basement Membrane is a narrow band of reticular tissue lying along the base of the epithelial cells to which it is securely adherent. It is normally well defined over both the placental and reflected parts of the amnion.

c. The Compact Layer. A relatively dense, acellular layer lying immediately deep to the basement membrane, to which it is densely adherent and from which it cannot normally be separated (Fig. 17). It is, like the basement membrane, more easily seen in heavily stained sections. The resistance to leucocytic infiltration displayed by the compact layer serves to define its limitations very accurately when a severe inflammatory response is present within the membranes.

d. The Fibroblast Layer is the most complex of the five amniotic layers. It is composed of a fibroblast network set in a mesh of reticulin. The only cells normally present are fibroblasts and Hofbauer cells (macrophages). Under normal circumstances it forms a considerable part of the thickness of the amnion.

e. The Spongy Layer, which is composed of the extra-embryonic cœlomic reticulum, forms the fifth layer. It is made up of a reticular network whose many collagen-like bundles were considered for
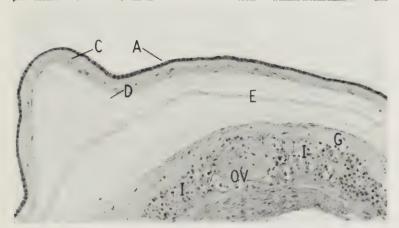
FIG. 17. Human amnion and chorion. A vertical histological section through amnion (above) and chorion (below). Compare with Fig. 16. A = epithelium, C = compact layer, D = fibroblast layer, E = spongy layer, G = reticular layer, = trophoblast, OV = obliterated villus. Note the fine reticular tissue connecting the spongy layer with its adjacent structures. Hæmatoxylin-eosin (×90).

many years to consist of elastic tissue. It is capable of great distension (Fig. 17). The mucus contained within its structure enables the layer to alter its shape with great ease and is responsible for what might well be its major function—to permit the amnion a surprising degree of movement upon the underlying fixed chorion.

Depth

The thickness of the amnion varies greatly, mainly due to alterations in the amount of mucin and fluid contained within the spongy layer. The loose connective tissue of this layer is capable of extreme variation, so that the membrane, which is normally 1/50 mm. to $\frac{1}{2}$ mm. thick, may increase its width by several hundred times and may be as much as 2·5 cm. in depth.

Blood Supply

The amnion at term does not have a blood supply. Blood vessels cannot be demonstrated within the layers of the amnion at any stage of pregnancy.

Nerve Supply

A nerve supply has been described in the amnion but these findings have not been confirmed.

Lymphatic Vessels

The possibility that the amnion contains lymphatic vessels is discussed by Hanon, Coquoin-Carnot and Pignard (1955) in their interesting book "Le Liquid Amniotique". Very many large spaces are present between the bundles of the reticular fibres of both the fibroblast and spongy layers but actual lymphatic vessels have not been observed either at low or high magnification.

Layers of the Amnion

The Epithelium

Shape. The epithelium is composed of a single layer of cells attached at their base to a basement membrane. The cells are mostly cuboidal in shape, but flattened almost pavement cells are often found in the reflected amnion, and columnar cells are frequently present in the placental amnion. None of these types is confined specifically to any one area.

Bautzmann and Schroder (1953) consider that the columnar cells are a deformity of the cuboidal cells, resulting from contractions of the basement membrane, which squeeze the base of the epithelial cell into a smaller area so that it becomes columnar in order to accommodate its own volume. Such deformity, however, is slight and only occurs at bends of almost 180 degrees (Fig. 18). Reconstruction of the fœtal sac after delivery indicates that some reduction in its area does occur either during or after parturition. Repeated examination shows that reductions in dimensions are mainly the result of contraction of the chorion. The fifth, or spongy, layer of the amnion allows free movement of the amnion upon the chorion so that apparent alteration in the size of the amnion is achieved by folding of the membrane and therefore very little reduction of the actual surface area.

The Apex. The inner surface or free edge (apex) of the cells is slightly convex in shape. In normal cuboidal epithelium the cells are uniform in height and regular in shape. Small evaginations of the cell membrane protrude from the free surface as microvilli to form a brush border. Microvilli have been described in the amniotic epithelium of animals (Bondi, 1905; Mandl, 1906). The brush border is composed of microvilli and occurs at the apex or free margin of the cell and is in contact with amniotic fiuid. Adjacent cells are joined near their apex by condensations or terminal bars so that the lateral surfaces of the cells are intricately welded together by a series of intercellular bridges (Bourne, 1962).

FIG. 18. This photograph illustrates how a fold in the amnion may cause the epithelial cells to assume a columnar shape in the concavity and a cuboidal shape on the convexity of the curve. Hæmatoxylin-eosin ($\times$ 300).

The Base. The base or outer edge of the cells, when examined at low power, is flat where they lie on the basement membrane. At higher magnification the basal region of the cells is very complex and is irregular in outline, forming irregularly shaped processes of various sizes (*basal processes*) between which are situated spaces of different size and shape. These processes, first observed by Danforth and Hull (1958) are in intimate contact with the basement membrane to which they are densely adherent (see Figs. 25 and 31).

The Side. Along the lateral aspect of the epithelial cells the two membranes of adjacent cells delimit the intercellular canals which are composed of a complex series of irregularly shaped vacuoles joined together by narrow channels. These lateral vacuoles frequently invaginate the side of the cell to give the impression that they lie deeply in the cytoplasm.

The Surface. The cells appear as an irregularly arranged mosaic. They are polygonal with rounded corners, having from three to six sides according to the shape of their immediate neighbours. Apparent openings, which are less than one-tenth of the diameter of the epithelial cells, occur at the junctions of the cells though they are occasionally found along the sides of the cells. They are probably

formed by the dilated upper ends of the intercellular canals, though the actual channel joining the intercellular canals to the amniotic cavity is very small and is visible only by high magnification with the electronmicroscope (see Fig. 27).

The Nuclei. The epithelial cells normally contain a single nucleus. The nuclei of the cuboidal cells are large, situated just above the centre, and are about one half of the diameter of the cell. In the columnar type of cell, found most frequently over the placenta, the nuclei may be either basal or apical. They contain one or more nucleoli. Their general appearance under low-power magnification suggests that they are roughly spherical with a well-marked nuclear membrane. Under high magnification, however, the nucleus is seen to have a very irregular crenated outline with a distinct but less well-marked nuclear membrane. The extensive folds of the nuclear membrane frequently delineate deep clefts in the nuclear substance. Fenestration of the nucleus may occur, giving the erroneous impression that intranuclear vacuoles are present. No true vacuoles have been observed in normal nuclei but degenerating areas in abnormal nuclei may fail to stain and give the impression that the nucleus is vacuolated.

Multinucleate cells are occasionally present. They are two or three times as large as a normal cell and contain from six to twelve nuclei arranged in the form of an irregular ring.

Mitotic figures in the amniotic epithelium are rare and have been described by Bautzmann and Hernstein (1957), Petry and Damminger (1956) and Keiffer (1926). It is now certain that multiplication of amnion epithelial cells is by a process of mitotic division, as may be seen easily in tissue culture of the amniotic epithelium (Bourne, 1962).

The Vacuoles. Vacuoles are invariably present in the epithelial cells. They may number from only a few to fifty or even more and they vary greatly in size. Sometimes they appear to distend the whole cell, pushing the nucleus to one side, to form balloon or goblet "cells", which have been considered to have secretory activity. In actual fact the majority of such goblet "cells" when examined at high magnification are found to consist of a distended intercellular canal.

The majority of vacuoles in the normal epithelial cells are surrounded by cell membrane because they are invaginations of the lateral cell membrane and are, therefore, an integral part of the highly complex system of intercellular canals.

A percentage of all vacuoles stain with fat stains, but the electronmicroscopic appearance suggests that the number actually containing

lipid is relatively small, and varies considerably from cell to cell. Hanon *et al.* (1955) agree that the amnion contains large quantities of fat.

Epithelial cells undergoing pathological changes invariably contain large and numerous vacuoles (Bourne, 1962).

The Cytoplasm. The cytoplasm is fairly uniform in structure except where it is replaced by the vacuoles mentioned above. Fat stains demonstrate the presence of small droplets of lipoid within the cells. The size and number of the lipoid droplets varies greatly from cell to cell, from one area of the membranes to another and also from one patient to another. Several authors, notably Keiffer (1926), consider that the fat is a precursor of the vernix caseosa, an opinion with which Hanon *et al.* (1955) do not agree. Early in pregnancy the amnion epithelial cells contain abundant glycogen but, at term, practically none is present (McKay *et al.*, 1958).

The Basement Membrane

The second layer of the amnion conforms to the definition of a basement membrane in that it is composed of a narrow acellular band of reticular tissue to which the epithelial cells are firmly adherent. Upon its deeper aspect it merges with the compact (third) layer of the amnion from which it cannot be separated.

The basement membrane stains densely with silver impregnation techniques and is easily seen in hæmatoxylin and eosin stained sections as a narrow, eosinophilic band along the base of the epithelial cells. The layer varies in thickness, usually being better marked and more definite over the placenta than over the reflected amnion, though sometimes it may be virtually invisible over both areas.

The attachment of the basement membrane to the compact layer is firm and complex. The density of the attachment of the basement membrane to the epithelium is probably due to the complicated invaginations that exist between these layers (Fig. 25). Protruding from the superficial surface of the basement membrane is a complicated system of prolongations that penetrate into the epithelial cells so as to interdigitate and lock with similar processes in the base of the epithelial cells. This complex system effectively increases by many times the surface area of the base of the epithelial cell and the basement membrane. It is probably of considerable physiological significance that the basement membrane evaginations and the basal processes of the epithelial cells are more complex and most numerous

in the region of the epithelial intercellular canals. At high magnification, the exact demarcation of the basement membrane and compact layer is difficult to discern.

The Compact Layer

The compact layer is a comparatively thin but relatively dense layer and accounts for most of the strength of the amnion. The layer can be handled after dissection from its neighbours as a definite membrane of uniform density and depth. It is firmly adherent to the basement membrane which lies on its inner surface and is loosely attached to the fibroblast layer on its deeper aspect. It is composed of a very intricate and complicated meshwork of reticular fibres arranged in bundles of varying diameter which form a complex and closely woven mesh (Fig. 31). Its strength results from its composition, structure and density, and these factors combine to make the compact layer responsible for most of the tensile strength of the amnion. Minute spaces which are filled by mucus are formed by the mesh. When tension is applied to the layer the fibres, which travel in every direction, alter the shape of the mesh rather like a piece of expanding wooden latticework.

The compact layer is normally devoid of cells. It appears to resist, to some extent, penetration by maternal leucocytes which, in advanced chorioamnionitis, may be seen along its deeper aspect. As the severity of inflammatory response in the amnion increases the white cells manage to penetrate the compact layer but, even then, a dense line of leucocytes along its outer surface will satisfactorily define the extent of the layer.

Fibroblast Layer

This layer forms the main thickness of the amnion. It varies in diameter from 0·05 to 0·5 mm. and is responsible for some of the alterations in depth which occur in normal amnion. Embryologically it is derived from extra-embryonic mesoderm compressed to form the extra-embryonic somatopleure by the enlarging extra-embryonic cœlom.

The histology of the fibroblast layer can only be studied satisfactorily by phase-contrast microscopy or at high magnification, although its presence can readily be seen on routine cross-sections where it appears as a pale eosinophilic band containing spindle-shaped nuclei. The layer is difficult to stain owing to its high mucin content. It is composed of a loose fibroblast network surrounded by an extensive reticular mesh.

The fibroblasts have an eccentric oval, disc-shaped nucleus containing one or more nucleoli. The long axis of the flattened nucleus always lies parallel to the epithelial surface of the amnion, so that its discoid shape is not appreciated when examining cross-sections in which the nucleus has an oval or spindle shape. The outline of the cells is altered by cellular processes which project from the main body of the cell. They are stellate or fusiform but vary considerably in shape and also, to a lesser extent, in size.

The cellular processes, which number from two to eight, may vary in outline from very short and blunt to elongated projections extending for many millimetres. The fibroblast processes do not conform to any definite pattern but their apparently haphazard arrangement forms an even network which on phase-contrast microscopy is indistinguishable from a true syncytium. Small granules are scattered irregularly throughout the cytoplasm of the cells and small vacuoles are often present in the peri-nuclear region. These cells have phagocytic properties which can be readily demonstrated by examining meconium-stained membranes. The meconium is concentrated in the vacuoles. Examination of meconium-stained membranes at high magnification by means of the electron microscope confirms that the fibroblasts do phagocytose foreign material (Bourne, 1962).

The response of the cellular processes to applied stresses is similar to that observed in the reticular network, for when tension is applied to the edge of the fibroblast network it alters its shape by elongation and narrowing of the processes so that they tend to lie parallel to the applied force (Fig. 19).

The reticular mesh is composed of fine fibrils together with coarse bundles of fibres. The former certainly do, and the latter may, arise from the fibroblasts (Bourne and Lacy, 1960). It is similar in structure to, but less dense than the compact layer. Fibres undoubtedly pass from the fibroblast layer into the compact layer to weld the two strata closely together (Fig. 31).

Hofbauer cells which are also present in this layer (Fig. 19) are distinguished from the fibroblasts by their rounded outline.

The Spongy Layer

The fifth layer of the amnion is called the spongy layer because it is naturally distensile.

Embryology. This portion of the amnion is the tissue of the extra-embryonic cœlom which has been compressed between the chorion and the enlarging amniotic sac. Morphologically one would expect
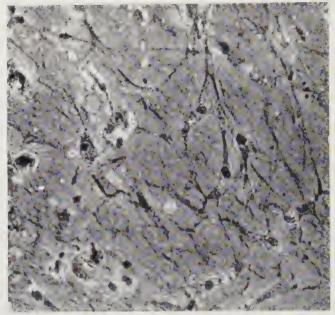
FIG. 19. *Amnion*. Fibroblast layer. The fibroblast network is visible against the reticulin mesh. A large Hofbauer cell is present to the left of lower centre. Many meconium inclusions, are present in the branching fibroblasts. Phase contrast ($\times$ 500).

the layer to be adherent to both amnion and chorion and this is in fact so, although adhesion to the amnion is more definite, especially over the reflected membranes. The presence of a fifth or spongy layer along the dividing membrane of uniovular mono-chorial twins also gives support to the principle of accepting the classification of this layer as part of the amnion rather than the chorion.

Histology. The spongy layer varies greatly in thickness, being as narrow as 5μ when compressed, especially over the placenta. Alternatively the layer may be distended by œdema to a width of 10 mm. It consists of an intricate, fine, fibril network bathed in mucus, which renders staining difficult but which, as one might expect from its origin, is very hygroscopic and will absorb large quantities of fluid to become thick and œdematous.

It is this layer with its wavy bundles of reticulin (Fig. 20) that has been described as containing elastic tissue. The fibres have an

Fig. 20. *Amnion.* Spongy layer. Phase-contrast photomicrograph showing both wavy and straight fibres. It is this type of wavy fibre that has been described as elastic tissue. (× 650).

elastic property but elastic tissue has not been observed, neither is there any muscle such as exists in the chick and reptile embryos.

Two types of cell are present in this layer, fibroblasts and Hofbauer cells.

The fibroblasts (Figs. 21 and 31) are fusiform or stellate cells containing a single oval nucleus and measuring from 20 to 40μ in diameter. Bundles of wavy and also straight fibres arise from the

Fig. 21. *Amnion*. Spongy layer. Phase-contrast photomicrograph. A fibroblast is seen on the right from which wavy fibres are rising. A group of Hofbauer cells is present on the left. ($\times$ 500.)

ends of these cells, which are scattered irregularly throughout the layer. They do not normally phagocytose material but, like the cells of the fibroblast layer, they can act as macrophages.

The Hofbauer cells in this layer are usually in groups of six or more, though they may occur singly.

The overall appearance of the spongy layer on cross-section is that it is composed of fibres that wave and undulate in a plane at right angles to the surface epithelium. The reticular network of this layer is complicated.

Function. The spongy layer, which morphologically is neither amnion nor chorion, must have an important function to support its preservation as an entity until late in pregnancy. If substances pass between the fœtus and the mother, directly across the fœtal membranes, then this layer can only act as yet another barrier— no matter how small. Perhaps it is a selective barrier, though there is no evidence to support such a supposition.

There are, however, two known properties of this layer that may have some functional significance. Firstly, it enables the amnion to move upon the chorion which is firmly attached to the uterine wall. This important function is of considerable clinical interest, because it enables the amnion to remain unruptured throughout the taking up and dilatation of the cervix in labour. There is, undoubtedly, some shearing of the chorion (and probably decidua) from the lower uterine segment in early labour but, as the cervix dilates the lateral tension increases and the chorion usually tears; the amnion, on the other hand, can move freely upon the chorion and is not therefore subjected to the same lateral tension as the chorion.

The second property of the spongy layer is its ability to distend with fluid and so vary its diameter. When the layer is enlarged it appears to be suspended midway between the chorion and the remainder of the amnion and this appearance led German workers to describe it as the "in between" or "floating" layer. It is attached to the adjacent layers by a very fine reticular network that fills the apparently empty spaces between the layers. Thickening, or œdema, may occur over large or small areas and the resulting uneven depth is most frequent in the amnion of the lower segment and placenta.

The significance of this change is unknown. It may result from trauma, or tissue reaction to stimuli such as infection or irritation. It might alter the mobility of the amnion upon the chorion, effectively change the permeability of the layer or act as a temporary area of storage.

Cyclic Changes

Kieffer (1926) attempted to explain the various appearances of the epithelial cells of the amnion by ascribing to them a cyclical secretory activity. According to Kieffer's observations the cells of the "presecretory" phase were flattened and contained large nuclei; the cells then entered the "secretory" phase when they became columnar, containing many vacuoles and apical nuclei. They finally

entered the phase of "elimination" in which they were flattened and eventually desquamated. Kieffer considered that most of the amniotic fluid and the vernix were formed by the amniotic epithelium.

It is almost certain that Kieffer was describing one of the processes which precede cellular death in the amniotic epithelium. Such cells, or their remains, are shed into the amniotic fluid. It is almost certain that desquamated cells are not replaced in the later stages of pregnancy, and it is improbable that they are adequately replaced even in early pregnancy. It seems as though the mitotic ability of the amniotic epithelium, which is at its greatest in the first half of pregnancy, is insufficient to repair the larger areas of cellular death. A cyclical change in the amniotic epithelium which includes cellular desquamation is therefore difficult to accept.

Furthermore, there is no actual proof that these cells do in fact secrete material into the amniotic sac although there is quite a lot of indirect evidence of their secretory activity.

The Chorion

The chorion, being the outer of the two human fœtal membranes, is in contact with the amnion on its inner aspect and the maternal decidua on its outer aspect. The enlarging chorionic sac is in immediate apposition to the decidua capsularis until, at about the 12th week of pregnancy, the true uterine cavity is obliterated, after which time it is separated from the parietal decidua by the now thin attenuated layer of decidua capsularis.

The superficial layers of the chorion overlying the placenta will, for the sake of brevity, be called the *placental chorion*, which even if biologically incorrect, is a very convenient term. The blood vessels contained in this area will be described. The remainder of the chorion is referred to as the *reflected chorion*. The portion overlying the internal os of the cervix is known as the *dependent chorion*, which may occupy any part of the chorion in relation to the placenta.

The chorion is composed of four layers, shown diagrammatically in Fig. 16. They are:

f. The Cellular Layer. This is a narrow layer consisting almost entirely of an interlacing fibroblast network similar to that present n the fibroblast layer of the amnion. The layer is more easily demonstrated in the earlier embryo than at term, when it may be absent.

g. The Reticular Layer. The reticular layer forms the major part of the reticular tissue of the chorion (Fig. 16). It is made up of a network of reticulin in which fibroblasts and Hofbauer cells (macrophages) are embedded. The layer maintains a fairly even width and it is unusual for it to be increased in diameter, even slightly, by œdema. Reticular fibres from this layer penetrate deeply into the trophoblast to bind the different chorionic structures together.

h. The Pseudo-basement Membrane. This layer is a narrow band of reticulin tissue forming the basement membrane of the trophoblast which lies upon its deeper surface. The name, pseudo-basement membrane, is used to avoid confusion with the basement membrane of the amnion.

i. The Trophoblast. This is a layer of trophoblast cells from 2 to 10 cells in depth. It is adjacent upon its deeper surface to the maternal decidua. Syncytio-trophoblastic tissue is not normally visible in the reflected chorion at term, although it is present earlier in pregnancy. The layer varies in depth, having no regular line of division from the cells of the decidua capsularis to which it is intimately attached. Not infrequently large plaques of the layer become necrotic and are replaced by deposits of fibrin-like material.

Atrophic, or ghost, chorionic villi which are lying within the layer are recognized as oval or rounded bundles of fibrous tissue embedded between the trophoblast cells (Fig. 16).

Depth

The reflected chorion varies in depth from 0·2 mm. to 0·02 mm. The variation is not as great as that seen in the amnion, where changes of up to one hundred-fold have been noted.

Blood Supply

The chorion at term contains, within its reticular layer, the fœtal arteries and veins as they pass between the umbilical cord and the chorionic villi of the placenta. These are normally present only over the surface of the placenta, but may also be found away from the placental surface in instances of velamentous insertion of the cord, succenturiate lobe of the placenta or placenta membranacea. There is no evidence to show that the chorion at term has a capillary blood supply for its own nutrition. In early pregnancy, whilst the chorion læve possesses actively functioning chorionic villi, there is a complex system of vessels throughout the reticular layer of all the chorion. As pregnancy advances, the villi of the chorion frondosum

develop into the placenta and simultaneously the villi of the chorion læve atrophy. The blood vessels supplying these atrophic villi also degenerate, but whereas the villi persist within the trophoblast layer of the chorion as atrophic, or ghost villi, the vessels disappear altogether.

Nerve Supply

There is no evidence that the chorion has a nerve supply.

Lymphatic Vessels

Both the reticular layer and the trophoblast contain relatively large spaces which lack demonstrable content when studied by light microscopy, but actual endothelial lined lymphatic vessels have not been observed.

Layers of the Chorion

The Cellular Layer

The first chorionic layer is morphologically the same as the fibroblast layer of the amnion, as both are derived from the extra-embryonic somatopleure. The layer is composed of a network of fibroblasts which is similar to that of the amniotic layer. The chorionic layer is very thin, being virtually only one cell thick. The cells have the same eccentric, flattened, oval nucleus which occupies a large area of the "body" of the fibroblast and is surrounded by small granules or, when the cells become phagocytic, by vacuoles.

Both large (multinucleate) and small (uninucleate) fibroblasts are present (Fig. 22). Their processes define a network of such clear definition that they give the false impression of forming a true syncytium. The processes themselves, and therefore the long axes of the cells, show a tendency to lie parallel as if under tension— a phenomenon observed also in the reticular layer of the chorion. These cells may assume macrophage activity. They phagocytose meconium which is then concentrated in vacuoles situated either in the perinuclear region or near the base of the cellular processes.

The reticulin structure consists of fine bundles of fibrils whose appearance suggests that they arise from the elongated fibroblast processes.

Cross-sections fail to give an accurate interpretation of the layer, which is most frequently seen in the earlier embryo but is invariably missing from the chorion when examined at term except in heavily meconium-stained specimens.
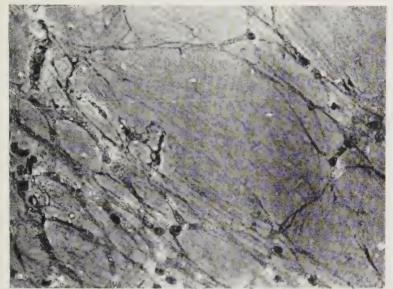
FIG. 22. *Chorion.* Cellular layer. Note the thin elongated cellular processes of the fibroblasts and the central location of the majority of the vacuoles. Both small and large fibroblasts are present, some of which appear to be multinucleate. Phase-contrast photomicrograph (× 450).

Reticular Layer

This layer forms the greater part of the thickness of the chorion and is responsible for most of the strength of that membrane. It varies in depth from patient to patient, but thickens as it nears the placenta and thickens still more over the placenta.

The trophoblast is densely adherent to the under surface of the layer, which tears easily.

The basic structure of the layer is a complex reticular network composed of both coarse and fine fibres. The coarse fibres have a tendency to lie parallel (Fig. 23) which may account for the relative friability of the layer. They do however branch repeatedly to form a latticework.

The cellular component of the layer consists of fibroblasts and Hofbauer cells. The Hofbauer cells are frequently phagocytic and may be filled with meconium in deeply meconium-stained membranes. The fibroblasts also assume phagocytic activity under certain circumstances and may also contain meconium-laden vacuoles.
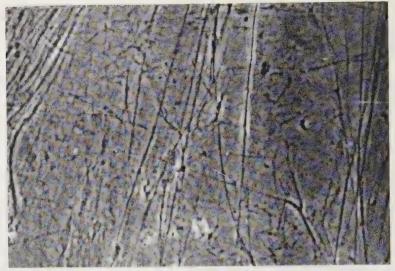
FIG. 23. *Chorion.* Reticular layer. The typical parallel formation of the fibres of the layer. A few narrow fibres run obliquely or at right angles to the main groups of fibres. "Nodes" are frequent. Phase-contrast photomicrograph ($\times$ 500).

Extensions of the layer form the core and stroma of both the placental and obliterated peripheral villi (the remains of the chorion læve) by evaginating into the trophoblast layer. The fœtal blood vessels are carried in the reticular layer of the chorion as they course over the surface of the placenta and they remain in the same anatomical and morphological layer as they enter first the main stem and then the secondary placental villi. There are no capillaries in the reticular layer as it overlies the placenta nor are there any blood vessels in the reflected parts of the layer in the later stages of pregnancy. The only exceptions to this are the membranes between the placenta and either a succenturiate lobe or a velamentous insertion of the umbilical cord.

The Pseudo-basement Membrane

This layer forms the basement membrane of the trophoblast that lies upon its deeper surface and to which it is firmly adherent. It is composed of a dense, reticular network whence branching fibres and fibrils travel into the trophoblast layer anchoring the two tissues firmly together. These fibres can be seen to travel for considerable

distances into the cellular trophoblast. The cells of the trophoblast layer can be removed from the pseudo-basement membrane by gentle scraping, leaving a roughened surface from which the obliterated chorionic villi protrude.

Superficially the layer is inseparable from the reticular layer. The component fibres of both layers intermingle to such an extent that the pseudo-basement membrane appears to be a condensation of the reticular layer. High magnification, however, confirms that the two zones are separate entities.

The pseudo-basement membrane itself contains no cells. It increases in density as pregnancy advances and is therefore more easily recognized at term. The increase is too indefinite for the layer to be used as evidence of maturity or postmaturity.

The Trophoblast

The deepest section of the chorion consists of from two to ten layers of trophoblast cells, which on one side are held to the pseudo-basement membrane by fibrils of the reticulin network and whose other side is in contact with maternal decidua. The cells are rounded, or polygonal where compressed by their neighbours, and contain a single dark nucleus within a pale staining granular cytoplasm. They vary greatly in size in an apparently haphazard distribution, although there is a definite tendency for the larger cells to occur near the pseudo-basement membrane whilst the smaller ones lie adjacent to the decidua.

The junction of the trophoblast and decidua is irregular and uneven, resulting presumably from the presence of villi in the chorion læve that invaded the decidua capsularis during the early development of the ovum.

The depth of the trophoblast layer does not vary much in the healthy state, and although it has a tendency to thicken near the placental edge, the actual transformation to the placental villi occurs as a fairly sudden change.

Circular or oval thin walled lymphatic-like spaces are occasionally present in the trophoblast layer but they do not have an endothelial lining. They may be used as a route of fluid transfer but their exact nature and function are unknown.

The remains of the chorionic villi mentioned above (Figs. 16 and 17) are present as "ghost" or residual villi. They are round bundles of pale staining fibrous tissue when cut in cross section, or if cut obliquely they appear to be oval, and occasionally a longitudinal section of an atrophic villus gives the impression of a band or rod

of fibrous tissue surrounded by trophoblastic cells. They take origin from the reticular layer of the chorion, which, in the formation of the chorion læve, protrudes through and carries a covering of the pseudo-basement membrane and trophoblast before it invades the decidua. The decidua capsularis, attentuated by stretching, is presumably unable to nourish the villi which then atrophy and are left as arbourizing excrescences upon the outer chorionic surface, embedded by pressure within the trophoblast layer and adjacent decidua, from whence they can be gently dissected after delivery.

A few fibrocytes are present in these atrophic villi although they contain no blood vessels or Hofbauer cells, but they are invariably surrounded by trophoblast cells. A syncytial layer has not been observed on the trophoblast of the reflected chorion at term. It is present in early pregnancy.

A type of pseudo-stratification is occasionally seen in the cells overlying the internal cervical os that has not been noted elsewhere. This is associated with degeneration of the amnion and premature rupture of the membranes.

Degenerative changes occur frequently within the layer, resulting in replacement of the cells by a granular fibrin-like material. Such areas are often associated with necrosis of the underlying decidua. These degenerative changes are diffusely scattered as irregular plaques of varying size over the membranes later in pregnancy but are frequently observed in the dependent membranes of premature infants. They are also found in pre-eclamptic toxæmia and postmaturity, but their association with premature membrane rupture may indicate a major cause of prematurity (Bourne, 1962).

The ultrastructure of the human placenta was first described by Dempsey and Wislocki (1953) and subsequently by others, including Boyd and Hughes (1954) and Wislocki and Dempsey (1955). Those interested in the anatomy, physiology and pathology of the placenta are referred to "The Placenta and Fetal Membranes" (1960) edited by Dr. Claude A. Villee, in which there are more than 2,700 references forming a very complete and classified bibliography.

The details of the circulation of amniotic fluid are not yet properly understood, but there now seems no doubt that the fluid enclosed within the amniotic sac must no longer be considered as a static pool. Exchange of both fluid and electrolytes occurs between the liquor amnii and the fœtus and also between the liquor amnii and the mother. The work of Plentl (1957) and Friedman, Gray, Hutchinson and Plentl (1959) has shown that large quantities of fluid per hour are moved from the amniotic cavity to the mother

at or near term and that there are differential rates for the transfer of various ions including sodium and potassium. There is no definite information to show exactly how such large quantities of fluid are moved from the amniotic sac to the maternal organism or to account for the passage of various ions at different rates. It is important to know if the membranes, particularly the amnion, are capable of active participation in transporting such large volumes of fluid.

The Electronmicroscopic Appearance of Mature Amnion

Epithelial Layer

At moderate magnification the cells appear to be covered by a single membrane which, on the surface next to the amniotic fluid, is evaginated into many small processes or *microvilli* (Figs. 24 and 26). Along the lateral aspects the two membranes of adjacent cells delimit a complex series of irregularly shaped vacuoles (*lateral vacuoles*). In the basal region the cell membrane is irregular in outline and

FIG. 24. Amnion epithelium. The upper, or free, margin of a portion of two columnar shaped epithelial cells from the placental amnion at term. Microvilli (M.V.) cover the surface of the cells. The nuclei (N) are irregular in outline. Intercellular canals (I.C.C.) extending from the free surface are dilated in places to form vacuolar-like spaces. Many smaller vacuoles are present in the cell cytoplasm. (✗ 6,500.)

forms irregularly shaped processes of various size (*basal processes*) between which are situated spaces of different size and shape (*basal vacuoles*) (Fig. 25).

Surface Microvilli. These do not appear to conform to a set pattern, as do those of the intestinal epithelium. The microvilli themselves are rather club-shaped, frequently having an ill-defined constriction near their base, distal to which the sides are parallel and the end rounded. The majority of the microvilli are single (*simple microvilli*) arising from the surface of the cell at irregularly spaced intervals. Sometimes the microvilli take origin in groups from a common base (*compound microvilli*). These may be from two to six, or even more, arising from a single base and these microvilli have a tendency to protrude at slightly different angles from their
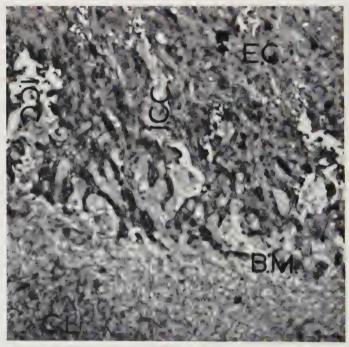
Fig. 25. Amnion epithelium. The base of an epithelial cell (E.C.) showing the basal processes which form a complex arrangement with the basement membrane (B.M.). Intercellular canals (I.C.C.) extend upwards between the cells. The compact layer (C.L.) of the amnion lies at the bottom of the photograph. (× 8,500.)
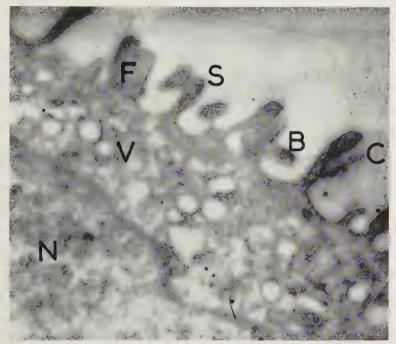
Fig. 26. Term amnion. The apex of an epithelial cell. Note the irregular arrangement of the surface microvilli, many of which have a constriction near their base. Simple (S), compound (C), branching (B) and fused (F) microvilli are present. There are many small vacuoles (V) between the nucleus (N) and the cell surface. A double membrane lines the nucleus. ($\times$ 66,500.)

common origin rather than to lie parallel with one another. The cell surface is raised by the rather large base from which the compound microvilli take origin and sometimes it forms a pedicle from whose apex the microvilli protrude. Branching and bizarre formations (*branching microvilli*) have been observed especially in compound microvilli arising from a pedicle. Occasionally adjacent microvilli fuse together (*fused microvilli*) (Fig. 26).

The microvilli are bordered by two closely applied membranes, each about 30 Å thick. Within the microvilli there are many fine rods which, due to the presence of a "clear" medulla and dense cortex are canal-like in appearance. The external and internal diameters of these canal-like elements varies; the maximum diameters recorded were 150 Å (external) and 70 Å (internal). When seen in

cross-section these elements simply appear to be placed closely together. Rarely, however, elements of similar composition are seen which exhibit the $9 + 2$ arrangement found in cilia and flagella (Bradfield, 1955). This suggests that occasional cilia exist alongside the microvilli. However, the possibility cannot be excluded that the $9 + 2$ pattern may occur in some microvilli perhaps during some stage of their development. The canal-like elements penetrate into the cytoplasm to a depth ranging from about $0.25\ \mu$ to $0.5\ \mu$ and it is due mainly to this that there appears to be a thin layer of slightly more dense cytoplasm immediately beneath the microvilli in cells examined at lower magnification.

Basal Processes. This term is used to describe the multiple prolongations which are present along the base of the epithelial cell. They reach into the basement membrane (Figs. 25 and 31) which is seen in the micrographs as a narrow layer of granular material. The basal processes do not extend into the deeper or compact layer of the amnion. The number and complexity of the basal processes increase in the region of the intercellular canals. The area between the basal processes is filled with material which is continuous with and similar in appearance to the basement membrane. This substance can occasionally be seen penetrating deeply into the epithelial cell and intercellular spaces (Fig. 25).

It seems logical that the epithelial cell should increase its basal surface area especially as the surface area of the apex of the cell is increased by the apical microvilli. Furthermore, if the intercellular canals are transporting material it is understandable that the basal area should be especially increased in the intercellular regions.

Lateral Vacuoles. The lateral vacuoles are a part of the intercellular canals that are present between adjacent cells. They form a complex and complicated system of spaces bounded by the lateral cell membranes and frequently invaginating the side of the cell to give the impression that they lie deeply within the cytoplasm (Figs. 24 and 27). Some of the vacuoles simply appear to extend into adjacent ones, whilst others are connected by fine channels formed by the close apposition of the two cell membranes (Figs. 27 and 28). Occasionally, tortuous communicating channels can be seen extending from the superficial end of the intercellular canal to open into the amniotic cavity (Fig. 27). The lateral vacuoles and intercellular canals therefore communicate directly with the amniotic fluid.

Projecting into some of the vacuoles are a variable number of microvilli, generally fewer per unit area than are seen on the surface of the cells. They are often very complex branching structures
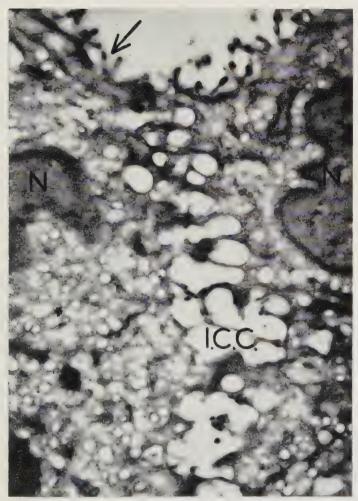
FIG. 27. Term amnion. A general view of an intercellular canal (I.C.C.) between two cells. The dilated portions of the canal are joined by narrow channels, one of which is opening into the amniotic cavity (arrow). Extensions of the intracellular canal extend into the cytoplasm. Many vacuoles are present in the cytoplasm. N = nucleus. (× 10,500.)
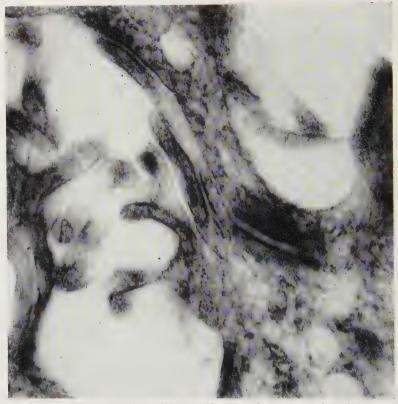
Fig. 28. Term amnion. High magnification of a portion of the inter-
cellular canal. Many microvilli protrude into the canal, the dilata-
tions (or vacuoles) of which are joined by fine channels. (× 75,000.)

(Figs. 27 and 28) having a tendency to occur more frequently in
those vacuoles near the centre of the intercellular canals.

The vacuoles in the lower parts of the cells are generally filled
with a substance of moderate density which is continuous with,
and similar in appearance to, the basement membrane (Fig. 25).
Sometimes a similar substance is present in vacuoles near the surface
of the cells which communicate with the amniotic fluid. In the
majority of instances, however, the vacuoles in the upper parts of
the cells lack demonstrable content.

The Cytoplasm. The cytoplasm of the epithelial cells appears
dense and granular and contains very few mitochondria.

FIG. 29. Term amnion. A high magnification of a basal process present in Fig. 10. Its structure is very complex, containing many fine channels. The spaces between the smaller projections of the basal process are filled with material similar to the basement membrane. (× 45,000.)

Some of the epithelial cells contain many small "empty" vacuoles (Figs. 24 and 26) scattered diffusely throughout the cytoplasm giving it a honeycomb appearance. The appearance of these particular cells suggests that they may have a specialized function. They are not to be confused with the appearance of the degenerating cell which is also diffusely vacuolated.

In some cells markedly dense bodies containing lipid are present (Fig. 27). Other cells contain spheroidal inclusions of varying size which are filled with amorphous material of moderate density. This may, in some instances, be glycogen (McKay *et al.*, 1958) but is more likely to be concentrated meconium-like material, since it is invariably present in meconium-stained membranes and corresponds to the meconium observed by light microscopy.

When studied at high resolution and magnification, comparatively large areas of the cytoplasm are seen to contain numerous paired parallel lines and circular elements (Fig. 30). These observations are interpreted as showing the presence of membranes arranged mainly in the form of fine canals with some occurring as parallel sheets. Examination of representative parts of the cell surface, where it borders the lateral and basal system of vacuoles, referred to above, reveals many circular apertures which communicate with the intracellular channels and canals.

The evidence suggests, therefore, that amniotic epithelial cells contain an extensive system of canals and channels which communicate directly with the extracellular space (Bourne and Lacy, 1960).

The Nucleus. The nucleus is a large, dense object usually located near the apex of the cell. It is irregular in outline, often with extensive indentations and sometimes fenestrated (Fig. 24). The structure undoubtedly accounts for the impression, by light microscopy, that the nucleus contains vacuoles. Definite intranuclear vacuoles within the nuclear membrane have not been observed by electronmicroscopy. The nucleus is bounded by a double membrane in which pores are visible at high resolution.

The Basement Membrane

The basement membrane is a thin layer, usually about $0 \cdot 1\ \mu$ in depth, consisting of a moderately dense substance which penetrates into the vacuolar-like indentations of the basal cell membrane (Figs. 25 and 31). It follows precisely the outer margin of the cell membrane and also fills the spaces between the basal processes. As stated above, the substance of the basement membrane appears to penetrate deeply into the base of the cell and a material whose general appearance is identical with that of the basement membrane is found frequently in basal vacuoles and occasionally in vacuoles higher in the epithelial cell.

The Compact Layer

The presence of the compact layer as a separate entity is confirmed. It is immediately subjacent to and closely adherent to the basement membrane. It is a moderately dense, granular layer composed of fibrils embedded in a matrix of almost equal density. It does not contain cells.

Connective Tissue. It is composed mainly of fibrils exhibiting faint transverse striations. Some of the fibrils are branched, the

FIG. 30. Term amnion. High magnification of a portion of the cytoplasm of the basal region of an epithelial cell (basal process). Fine canals are present which open into the vacuoles and communicate with the extracellular space. ($\times$ 100,000.)
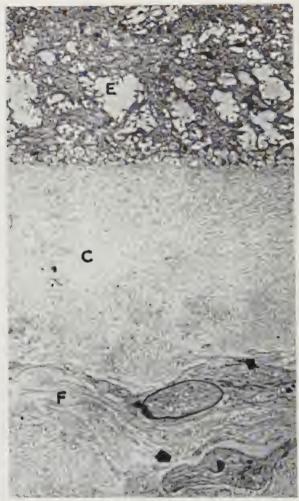
Fig. 31. Term amnion. Vertical section through part of the amnion. The epithelium (E) with intercellular canal, vacuoles and basal processes lies on the basement membrane, the compact layer (C) and fibroblast layer (F). A portion of two fibroblasts is shown at the bottom of the figure. ($\times$ 3,000.)

angle of branching usually being about 90°. They are arranged in bundles (not bounded by a membrane) lying in various planes. Thus in any one region a great number of parallel fibrils lie next to a comparable number of similar elements which have been sectioned transversely or obliquely. The morphological evidence, therefore, suggests that the fibrils are reticular fibrils. Typically in the spongy layer, the fibres have a wavy appearance; while this may be due to some contractions, its persistence indicates a wavy form to be the correct structure.

Fibroblasts. As far as can be determined from individual sections the fibroblasts within the fibroblast layer form a diffuse network. They do not form a syncytium. They are elongated, irregularly-shaped cells lying with their long axes approximately parallel to the basement membrane. Occasionally their shape is triangular or stellate. Along the surface of the fibroblasts are a few tiny pseudopodial-like projections (Figs. 32).

The fine structure of these cells varies, either because the cells are of different ages or because they are in different physiological or pathological states. The nucleus is a dense, irregularly-shaped mass which may sometimes be elongated and fusiform in outline.

Also present in most cells is a large single mass of material which is bordered by membranes of the endoplasmic reticulum. When examined at high resolution it is seen to consist of an almost clear matrix within which is a network of greater density. In some cells the network consists of fibrils embedded in a homogenous ground substance. In other cells the fibrils are scarce or absent, while within the ground substance are many vesicles. These observations seem to demonstrate quite definitely that some connective tissue fibrils are formed intracellularly. A similar observation was made regarding the stromal cells of the human placental villus by Wislocki and Dempsey (1955).

Parts of the cell surface, however, occasionally appear not to be covered by a membrane. Where this occurs there are many connective tissue fibrils projecting from the cell cytoplasm into the extracellular space (Fig. 33). There seems little doubt that these fibroblasts are actively synthesizing new fibres.

Particularly in the spongy layer the fibroblasts are even more elongated. Their ends are closely applied and this, together with the fact that the cells follow the wavy course of the connective tissue fibres, makes them appear to be articulated.

Macrophages. The macrophages of the fibroblast and spongy layers are the same as the Hofbauer cells. They are relatively scarce
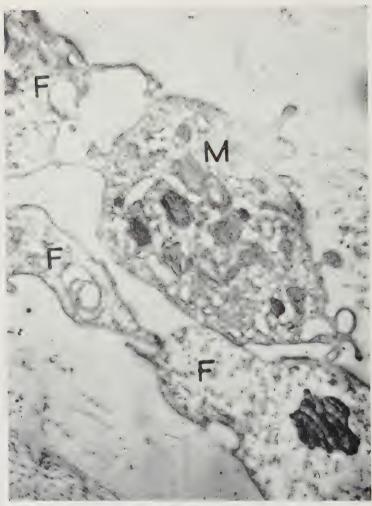
FIG. 32. Term amnion. Three fibroblasts (F) lying adjacent to a macrophage (M) or Hofbauer cell. At low magnification these cells appear to form a syncytium, but examination at high magnification shows that the cells are merely adjacent. Note the lipoid-like material in the lower fibroblast and the varying density of the many inclusions within the Hofbauer cell. There is a similarity between the pseudopodia of the two types of cell. (× 8,750.)

FIG. 33. Term amnion. Synthesis of connective tissue fibrils by fibro-blasts. F=Fibroblast. N=Nucleus. Part of the fibroblast cell surface on the right is not covered by a membrane. Connective tissue fibrils are protruding from the cytoplasm to join those of the surrounding tissue. (× 12,000.)

and are scattered diffusely throughout both the layers, often lying in a fairly clear space in the tissue and not infrequently adjacent to fibroblasts (Fig. 32). In many instances the cell membranes of the fibroblasts and macrophages are in contact.

The cells are roughly oval in shape but at higher magnification are seen to possess a variable number of tiny, irregularly-shaped pseudopodia-like processes. The nucleus is a large, dense oval structure. The detail of the cytoplasm alters enormously according to the activity of the cell, but the most prominent feature is the presence of very many vacuoles whose size varies greatly (Fig. 32). They may contain a variable quantity of lipid and sometimes hæmosiderin, but the majority of the vacuoles contain no demonstrable material in the resting state.

Amniotic Fluid Transport. So far as can be determined on a purely morphological basis, it seems likely that some of the amniotic fluid which passes from the fœtus to the mother and the accompanying differential rate of turnover of various ions may be brought about by the amnion. As a working hypothesis it may be conjectured that the fluid enters the amnion via (a) the opening between adjacent cells where it passes into the lateral system of vacuoles and (b) the upper surface, whose area is greatly increased by the presence of microvilli. Within the cells the fluid presumably enters the complex system of fine canals and channels. The fine canals and channels communicate with the lateral and basal vacuoles and hence with the extracellular space; this results in an enormous increase in surface area. Within the vacuoles there is presumably some mixing of any solution which may have entered via the two principal pathways. Assuming that some ions travel more readily along one route than the other, they could offer an explanation (although much over-simplified) of the differential rate of turnover of different ions. Having passed through the epithelium, the fluid must permeate the connective tissue layer. Since this layer consists mainly of a network of fibres there is no objection to this on morphological grounds.

Some Characteristics of the Amnion and Chorion at 12 Weeks Gestation

The Amnion

The epithelial cells are cuboidal in shape and somewhat smaller than the cell at term. The nucleus is usually a spheroidal structure devoid of the complexities so characteristic of later pregnancy.

Surface microvilli are present but are scanty in number. They are of a simple structure because the compound and branching microvilli (so commonly seen at term) are absent. The intercellular canals follow a fairly direct and easily traceable course in which vacuoles of relatively simple design are placed at irregular intervals. Fig. 34 is an oblique section through the epithelium and shows that the intercellular vacuoles vary greatly in size and shape. At this stage of pregnancy the formation of simple microvilli within these spaces is just commencing.

The basal region of the cells is also relatively simple. The basement membrane, which is thin, exhibits little or no tendency to invaginate into the cell and there are few basal processes.

The cytoplasm of the cells is not so dense as that of the cells at term. There are irregular, but well localized areas of granular material scattered throughout the cells. Mitochondria are numerous. Many small circular elements are scattered diffusely throughout the cells.
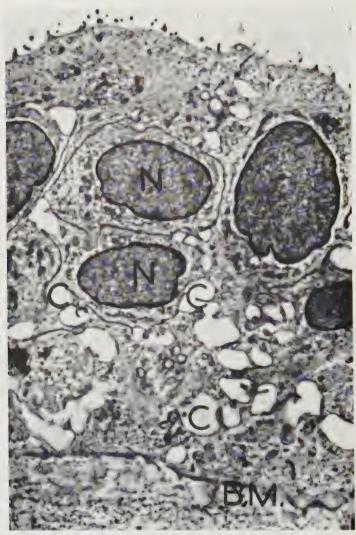
The connective tissue is composed mainly of reticular-like fibrils (similar to those present later in pregnancy) in which fibroblasts form a comparatively dense layer. They often lie in actual contact with neighbouring cells but do not form a syncytium. Their shape varies considerably and their cytoplasm contains large quantities of lamellar or tubular endoplasmic reticulum.

Occasional macrophages are present within the connective tissue. They are characterized by an oval or rounded outline and the presence of many tiny pseudopodia. Mitochondria are numerous but most of the cytoplasm is filled by vacuoles of various size whose contents differ considerably in their density to the electron beam.

The Chorion

A full description of the ultrastructure of the human placenta and immature chorionic villi has been published by Wislocki and Dempsey (1955), Boyd and Hughes (1954), Dempsey and Wislocki (1953) and others.

The connective tissue of the chorion at this early stage of pregnancy is similar to that of the amnion. The trophoblast consists of a layer of Langhans cells covered on its outer aspect by the syncytial trophoblast. The Langhans cells lie upon a well-formed basement membrane which is composed of fine fibrils embedded in a material of rather similar density. The basement membrane penetrates deeply into the Langhans cells at irregular intervals and, in addition, there are occasional small indentations in the base of

Fig. 34. Amnion at 12 weeks gestation. An oblique section of the amniotic epithelium showing the cellular structure. Surface microvilli and basal processes are not well formed. The intercellular canals are of relatively simple structure. B.M.=Basement membrane. N=nucleus. C=intercellular canal. (× 5,000.)

the cells which are also filled by basement membrane (Figs. 35 and 36).

The Langhans cells are easily distinguished from the overlying syncytial trophoblast by virtue of their relatively dense, granular cytoplasm and dark ovoid nuclei. Superficially the cells are covered by syncytial trophoblast. Projections of basement membrane frequently intrude into the basal portion of the intercellular space but no canals, as such, have been observed. Not infrequently the syncytium dips down between neighbouring Langhans cells to come into direct contact with the basement membrane (Fig. 35). The granular cytoplasm contains many mitochondria together with a variable number of irregularly shaped vacuoles.

The syncytium completely covers the Langhans cells. Its free surface is in contact with the intervillous space into which protrude a variety of microvilli (Wislocki and Dempsey, 1955). These are frequently long and slender (Fig. 36) arising at irregular intervals from the uneven surface of the syncytial trophoblast. Other sections contain short, rounded microvilli that give the impression of arising
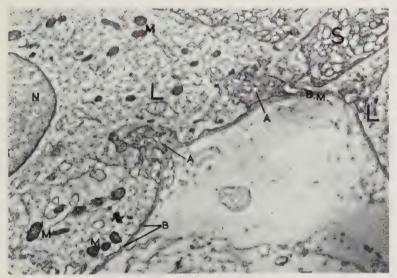
FIG. 35. Chorion at 12 weeks gestation. The syncytio-trophoblast (S) comes down to the basement membrane (B.M.) in between two Langhans cells (L). Invagination of the basement membrane protrude into the Langhans cells: these are large and complex (A) or small (B). N=nucleus. M=mitochondria. (× 6,500.)
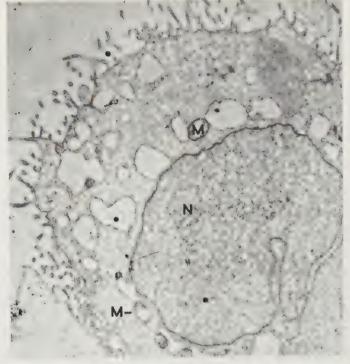
FIG. 36. Chorion at 12 weeks gestation. Microvilli on the surface of the syncytiotrophoblast. The large vacuoles and the cystic mitochondria (M) suggest early degenerative changes. N=nucleus. ($\times$ 12,250.)

by distension of the slender microvilli. In other areas the surface of the syncytium is smooth, microvilli being absent.

The nuclei are generally spheroidal but may sometimes be irregular in shape. The granular cytoplasm is filled almost completely by vacuoles which vary greatly in both size and content.

Conclusions

The structure of the amnion and the chorion at the 12th week of gestation is simple when compared with the complexity of this structure towards the end of pregnancy. These are two possibilities for this difference. Firstly, the amnion at the 12th week of gestation is surrounded, or has been surrounded until recently, by active chorion

so that the amnion itself has not yet been required to act as a medium for the transfer of fluid or materials between the fœtus and the mother. Secondly, it is possible that the role of the amnion in the physiology of pregnancy may change after the formation of the placenta, or with the increasing demands of the more mature fœtus.

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DIABETES IN RELATION TO OBSTETRICS AND GYNÆCOLOGY

by

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The evidence at present available suggests that the incidence of diabetes is rising. An accurate assessment of the incidence is difficult, or indeed impossible in many parts of the world. According to a communication from the Office of Health Economics published in 1964 there were 33,500 registered diabetics in England and Wales in 1941. In a study of 10 practices in and around Birmingham in 1962, the incidence was shown to be 6·4 per thousand of the population (College of General Practitioners). This rate is approximately ten times that shown in 1941, and applied to the whole population of England and Wales would give an estimated number of persons suffering from clinical diabetes as well over 300,000. This increased incidence may well reflect a greater accuracy in diagnosis, improved methods of treatment of both the primary metabolic disorder as well as of its vascular and renal complications, greater longevity, and a decreasing mortality from intercurrent diseases. The facts, nevertheless, are inescapable.

The concept of diabetes as a specific disease from which a patient suffers, or does not suffer, dates from the pre-insulin era. The discovery of insulin and the appreciation of the importance of diet, made it possible to control the hyperglycæmia and the ketosis which characterized the established disease. Death which so frequently followed within a few years of onset, therefore became preventable. Not so preventable, however, are the pathological complications of the disease, especially the renal and vascular disorders of long-standing diabetes. Still less do we know about the primary cause of the disease, or if there is indeed a single cause. A newer concept of this disease has in consequence developed, and we now recognize the existence of a metabolic disorder of carbohydrate tolerance, which may be present for many years before the onset of clinical

diabetes, perhaps even from birth. This metabolic disorder progresses slowly but surely as age advances. Butterfield (1964) has shown, in apparently normal individuals, that glucose tolerance decreases with age. Apart from ageing, however, there are other factors during life which impair glucose tolerance either permanently or temporarily, and many of these are of paramount importance to the gynæcologist. I mention particularly the hormonal changes associated with the onset of menstruation and the subsequent hormone variation that occurs with each menstrual cycle. Equally important is the menopause. The effects of overeating, of the development of obesity, of physical and emotional stress, and above all the effects of pregnancy, have to be considered.

For the diagnosis of clinical diabetes we must accept fairly rigid criteria: a fasting blood sugar in excess of 100 mg./100 ml., or a blood sugar in excess of 120 mg./100 ml. 2 hours after the ingestion of 50 g. of glucose (which is the standard glucose load). If this is taken to represent clinical diabetes, it is abundantly clear that there must be a vast borderland of mild deviations from normal glucose tolerance. The physician's interest in these borderline potential diabetics is no doubt great, but it is long term. The extent to which modification in either the mode of life or the dietary habits of a patient, who shows such minor deviations from normal glucose tolerance in youth, can affect the time and the mode of onset of clinical diabetes, or delay the vascular and renal complications, is as yet unknown.

To what extent is diabetes hereditary? Evidence points to the fact that approximately one-third of all clinical diabetics have a positive family history. If a child is born with an inborn error of metabolism, what is the exact nature of this error? Diabetic mothers give birth to babies sometimes overweight and overfat, but also sometimes normal or even small. Are those which are overweight more likely to possess the inborn error than those which are apparently normal? These and many other questions may not be answerable for another generation, because the maximum age incidence of diabetes is in the late fifties. Even the oldest of the babies of diabetic mothers born since the discovery of insulin have not yet reached the age of 40.

The obstetrician, however, is faced with a more urgent problem. The potential diabetic woman who becomes pregnant has, at present, a one in four chance of producing a dead baby, unless her inborn error can be detected during the course of her pregnancy, and even then the perinatal mortality cannot be reduced to normal. Several surveys of whole populations, using various screening tests, have been carried out within recent years and have shown that there are

not only many undetected diabetics, but also a large number of patients who, without having elevated fasting blood sugar levels, nevertheless show impairment of carbohydrate tolerance as judged by glucose tolerance tests. These people must be regarded as potential diabetics. Screening tests to cover an entire population will always be difficult and costly. Most women, however, have one or more pregnancies. This gives the obstetrician an unequalled opportunity to screen the large bulk of the female population during one or more antenatal periods. Pregnancy is particularly important for two reasons:

1. Pregnancy adversely affects carbohydrate metabolism and is therefore diabetogenic.
2. The obstetric phenomena which occur in a pregnant woman who suffers from established diabetes are just as likely to occur in a pregnancy many years before she develops the actual clinical syndrome.

The Effects of Pregnancy on Carbohydrate Metabolism

It is impossible in a chapter of this kind to discuss in any detail the complexities of normal carbohydrate metabolism, or the exact role of insulin and other hormone substances upon it. Hyperglycæmia and glycosuria are the most important evidence of impaired carbohydrate tolerance. In normal pregnancy an increased output of adrenocorticotrophic hormone is known to occur. It is probable that there is an increase in the output of growth hormone, which was shown by Young (1945) to be closely related to the pituitary diabetogenic factor. Secondary to increased activity of the anterior pituitary, there is an increase in the output of suprarenal glucocorticoids and other steroids. There is therefore a theoretical basis for impairment of glucose tolerance, insulin sensitivity and glucose utilization. Wilkerson (1959) estimated that abnormal glucose tolerance tests occurred in $6\cdot2\%$ of 17,000 unselected pregnancies, and reported an even higher incidence with the progression of pregnancy. Out of 134 negative tests in the first trimester $1\cdot5\%$ became positive in the second, and out of 1,253 negative tests in the second trimester 10% became positive in the third. Burt (1956) showed a decrease in insulin sensitivity which began about the 26th week of pregnancy and progressed steadily up to term. More recently Leake and Burt (1962) and Spellacy and Goets (1963) have shown an increase in plasma insulin-like activity during the last trimester of normal pregnancy. It is known that in pregnancy glycogen is more readily mobilized from the liver and conversely storage is delayed,

and that considerable modifications of the absorption rate of carbohydrate from the stomach may occur. However, rather disturbing differences have been found when oral and intravenous tolerance tests are compared in the same group of pregnant women. Thus Kaplan (1961) found that intravenous tests were quite normal in a group of women showing abnormal oral tests. Welsh (1960) investigated, by the intravenous test, a series of 27 pregnant women, who showed abnormal oral glucose tolerance tests and found that only 8 of these had abnormal curves. Love *et al.* (1964) showed similar figures in cases investigated early in the puerperium. The fact, however, that the intravenous tolerance test shows a lower incidence of abnormality, does not necessarily commend it as a better test.

Another factor that requires mention in regard to carbohydrate metabolism during pregnancy is the well-known tendency to a lowering of the renal threshold. This is partly associated with the physical changes in the renal blood flow, which lead to an increased glomerular infiltration rate, but there is also delay in the reabsorption of glucose from the renal tubules, due, according to Bergquist (1954), to the direct action of adrenocorticotrophic hormone.

We do not know whether the renal threshold is lowered in every pregnancy, but we do know that it is lowered very frequently in normal pregnancy as well as in pregnancy occurring in established diabetics. In some patients the renal threshold is unaffected and may, on occasions, actually be increased. A patient recently under my care never passed any sugar in the urine in spite of persistently elevated blood sugar levels. This may on occasion be manifest throughout pregnancy, but under other circumstances it is a transient episode as yet unexplained. From the practical point it adds still further to the difficulty of detecting impaired carbohydrate tolerance by merely relying upon the evidence of glycosuria. The true incidence of glycosuria in pregnancy is not easy to ascertain, since there is as yet no report of a well-controlled, sufficiently random survey from which to obtain reliable figures. Butterfield (1964) states that the incidence of glycosuria in the female population is about $2 \cdot 5\%$, but there is no doubt that during pregnancy this figure is exceeded. The incidence in the antenatal clinic at King's College Hospital is about 10% (excluding known diabetics), but this cannot be taken as a population incidence because the patients are not sufficiently random. Furthermore, the exact incidence cannot be determined from the 12–15 tests that are carried out during the course of the normal antenatal period, because the incidence will be found to vary according to whether the patient brings to the antenatal clinic

a specimen which she has passed first thing in the morning or whether she brings a specimen passed within an hour or two of a meal. There is need for an extensive survey of the incidence of glycosuria in normal pregnancy.

Diabetogenic Effects of Pregnancy

Apart from the evidence based upon the physiological changes of carbohydrate metabolism, there is much clinical evidence that pregnancy is diabetogenic. Pyke (1956) showed that there was a preponderance of women over men in diabetics over the age of 45 (Fig. 37). The preponderance of women over men was confined to
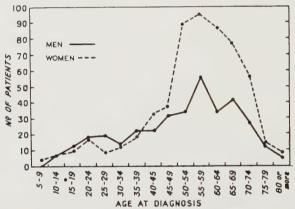
FIG. 37. Age distribution by sex of 953 diabetics. (Pyke, D. A. (1956). *Lancet*, **1**, 818)

those who had borne children. He further showed that, in women over 45, there was a direct relationship between the incidence of diabetes and parity. A recent population survey by Walker *et al.* (1964) showed that 3 out of 38 diabetic women had given birth to more than 10 children. This contrasted with a figure of only 13 out of 1,289 non-diabetic women who had given birth to more than 10 children. Fitzgerald *et al.* (1961) have also shown that the incidence of diabetes increases with each increase in parity. On the other hand, Jackson (1961) could find no evidence of impairment of glucose tolerance in normal pregnancy, having excluded as far as possible all patients suspected as potential diabetics as well as those who were known diabetics. He thinks that pregnancy is only

diabetogenic to those patients who have an inborn error of carbo-hydrate metabolism, whatever its nature, and who should therefore be classified as potential diabetics. He is supported by Tulloch and Cruickshank (1960) who found, at University College Hospital of the West Indies, that the parity of 300 diabetic women when com-pared with that of an age-matched group of non-diabetics, showed no statistical difference. They did, however, find that in the group with 10 or more pregnancies there was a preponderance of diabetics. If parity plays such an important role in the ætiology of diabetes, one might expect that in countries where high parity is frequent, the incidence of diabetes in later years would be higher. Conclusive evidence on this point is at the present time lacking, but a recent survey by Yen (1964) is of great interest in this connection. He investigated 442 pregnant women in the island of Guam. In this community extremely high parity is the rule, and a very large number of patients have 10 or more pregnancies. He found positive screening tests in the remarkably high incidence of $16 \cdot 7\%$ of his 442 patients. He used the oral glucose tolerance test, but gave 100 g. of glucose instead of 50 g. and took a "normal" figure of 150 mg./100 ml. at 2 hours instead of 120 mg./100 ml. More important, however, than the high incidence of positive screening tests was the fact that, of those who showed positive tests, $28 \cdot 7\%$ were still abnormal 6 weeks postpartum, and $5 \cdot 4\%$ of these had become frank diabetics. He also made the interesting observation that the incidence of abnormal glucose tolerance tests in pregnant women over 40 was seven times greater than in women of 20. The weak point in this survey is that the population investigated live in a small isolated island com-munity where inbreeding as well as high parity must be frequent. The relative importance of heredity and high parity therefore cannot be clearly differentiated in this survey. Furthermore, the finding of impaired glucose tolerance in the older age group does not prove whether this is due to increased parity or to increased age. It may be that both factors are important.

There are two other pieces of important evidence of the diabeto-genic nature of pregnancy. Firstly, it has been known for many years that clinical diabetes commonly manifests itself for the first time during pregnancy (Bowen and Heilbron (1932) 27%; Lawrence and Oakley (1942) 27%; and many others). Secondly, many authors have referred to cases of temporary clinical diabetes or sub-clinical diabetes, diagnosed only by abnormal glucose tolerance tests, which occur during the course of a particular pregnancy but which disappear as soon as the pregnancy is over. It is usual for a similar

departure from normal carbohydrate metabolism to be repeated in successive pregnancies and, in the ultimate, these patients nearly always develop permanent diabetes (Peel, 1962).

Pre- or Potential Diabetes

The concept of pre-diabetes was first made by Allen (1939). He showed that in the years preceding the onset of clinical diabetes, diabetic women tended to give birth to abnormally large babies and to have a high perinatal mortality. Many authors since then have confirmed these findings (Gilbert and Dunlop, 1949; Miller *et al.*, 1944; Oakley and Peel, 1949; Hagbard, 1958). Currently the perinatal mortality in so-called pre-diabetic pregnancy is about 25%, and the incidence of babies weighing over 10 lb. (4·5 kg.) even higher. In many ways the term pre-diabetic is an unsatisfactory one, because it can only be made retrospectively after the patient has developed clinical diabetes. A prospective study was made by Fitzgerald *et al.* (1961) and they investigated a series of women who had given birth to babies weighing over 10½ lb. (4·75 kg.) 13 or more years previously. More than 50% of those women who were over 45 years of age showed abnormal glucose tolerance curves. It remains unexplained why, if pregnancy is diabetogenic, there should be this time lag between the termination of pregnancies and the development of clinical diabetes at or over the age of 45.

Because of the confusion that has been created by the use of the term pre-diabetes as applied to women, who may in fact never develop the clinical disease, the Medical and Scientific Section of the British Diabetic Association has suggested a modified classification and introduced the term potential diabetes with the following definition:

"Potential diabetes." This term is applied to the patient who, with a normal glucose tolerance test, has potential risk of developing diabetes because:

(*a*) She is an identical twin, the other twin being diabetic.
(*b*) Both her parents are diabetic.
(*c*) She has one diabetic parent and the other (non-diabetic) parent had either a diabetic parent, sibling or offspring or a sibling has had a diabetic child.
(*d*) She has given birth to a live or stillborn child weighing 10 lb. (4·5 kg.) at birth or a stillborn child showing hyperplasia of the pancreatic islets not due to Rhesus incompatibility.

Such a classification may be reasonable from the medical standpoint, but in some ways it is a pity that it has been drawn up without reference to obstetrics. This classification is quite unsatisfactory to the obstetrician because the possibility of the patient being a potential diabetic has to be considered during the antenatal period in a very much wider group of patients. I think that investigation of carbohydrate metabolism is necessary during the antenatal period in any pregnant woman who falls into one of the following ten categories:

1. A family history as defined above.
2. Glycosuria.
3. The development of unexplained hydramnios in the last three months of pregnancy.
4. Unexplained intra-uterine fœtal death.
5. Unexplained early neonatal death, especially in association with the respiratory distress syndrome.
6. Unexplained prematurity.
7. A baby who is appreciably overweight for its maturity.
8. High multiparity.
9. Progressive pregnancy obesity.
10. Patients who have given birth to babies with repeated congenital anomalies.

If giving birth to babies weighing more than 10 lb. (4·5 kg.) is the only reason for investigation then many potential diabetics will be overlooked, and many obstetric misfortunes will be allowed to occur. Careful investigation of the potential diabetic during the antenatal period will increase the number of cases that are detected.

Screening Tests for Potential Diabetes

A fasting blood sugar should be taken as an initial screening test in patients falling into any of the above categories and secondly a blood sugar estimation should be performed 2 hours following the ingestion of 50 g. of glucose by mouth. If the fasting blood sugar is below 100 mg./100 ml. and the 2-hour figure below 120 mg./100 ml. there is no point in carrying out a full glucose tolerance test, unless the 2-hour level is more than 20 mg. higher than the fasting level.

The position at the present time with regard to glucose tolerance tests is far from satisfactory. There is much evidence to suggest that a more reliable oral test would be obtained if 75 g. or even 100 g. of glucose were given as the glucose load. On the other hand,

I have already mentioned that oral glucose tolerance tests show a very much higher incidence of abnormality in pregnancy than do the intravenous tests. The intravenous test has the advantage of rapidity and of avoiding the variable factors associated with glucose absorption from the alimentary tract. On the other hand, the problem of the intravenous injection of 50% glucose is not without its local complications, and the fact that it reveals a lower rather than a higher incidence of impaired glucose tolerance in pregnancy makes it a less sensitive test. At the present time it is better to be alerted by a disordered oral test than to be lulled into a sense of false security by a normal intravenous one. The risk of interfering with what would otherwise be a normal pregnancy on the strength of an abnormal test must be weighed against the failure of interference which might follow the finding of a normal intravenous test. The introduction of the intravenous tolbutamide test has not, in fact, so far contributed anything very important. Kaplan (1961) concluded that an abnormal oral glucose tolerance test was usually associated with an abnormal intravenous tolbutamide test, but that the intravenous glucose tolerance test in the same patient was often normal.

Because of the contradictory results of these various screening tests, Fagans and Conn (1954) introduced the so-called stress curve. They administered 50 mg. of cortisone acetate $8\frac{1}{2}$ hours and again at 2 hours before performing the standard glucose tolerance test and claimed that, in 104 controls, a normal curve was converted into an abnormal curve in only 3%, whereas in 295 non-diabetic relatives of diabetics, an abnormal curve was found in 25%. Gotto *et al.* (1960) used 10 mg. of prednisolone instead of cortisone acetate, and Joplin *et al.* (1961) described a prednisone glycosuria test. These tests have not yielded such a consistent result as was initially expected. They are quite useless during pregnancy, because of the increased endogenous cortisone already existing. They can, however, on occasions be very valuable, in that a curve completely normal during pregnancy may be revealed as a grossly abnormal diabetic type curve if repeated later following the administration of cortico-steriod. Fig. 38 shows an example in which the cortisone stress curve was of diagnostic significance. The practical points are these:

1. Investigations should be delayed until the last 3 months of the pregnancy in patients suspected of being potential diabetics from history or present findings.
2. The immediate postpartum period is not the best time for investigation of carbohydrate tolerance.
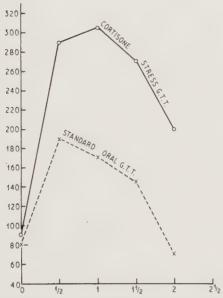
Fig. 38. Glucose Tolerance Tests 8 weeks postpartum in a patient who was delivered a premature stillborn baby at 38 weeks. Normal GTT during pregnancy.

3. The well-known phenomenon, in the established diabetic, whereby the insulin requirement drops abruptly after termination of the pregnancy must be remembered in this connection.

4. It is wise to delay investigation for from 6 weeks to 8 weeks after delivery.

Sometimes, however, when the glucose tolerance test is normal during pregnancy, action may have to be taken upon the results of the clinical examination and a suggestive obstetric history, rather than relying upon the results of the biochemical test.

Obstetric Phenomena of the Potential, Pre- and Established Diabetic

It is a remarkable fact that the obstetric phenomena tend to be identical, whether the patient is an established diabetic or whether she is in the potential or pre-diabetic phase, and consideration will now be given to the more important of these phenomena.

Fœtal Macrosomia. It is generally accepted that although the range of variability is wide in individual cases, the mean birth weight of the babies of diabetic and pre-diabetic mothers is considerably in excess of the non-diabetic. Hagbard (1958) gives the figure of 550 g. and Hsia and Gellis (1957) found the difference to be 500 g. Cardell (1953) found that there was no difference in the birth weight of babies of similar gestational age up to 219 days between the babies of diabetic and non-diabetic mothers. The increase occurs in the last 60 days of pregnancy. There is a marked hypertrophy of the islet tissue of the pancreas in the baby of both diabetic and pre-diabetic mother. Cardell (1953), from postmortem examinations, estimated that the increased islet tissue of the pancreas of the baby of the diabetic mother was approximately four times that of the normal. He further showed that there was a direct correlation between the amount of islet tissue hypertrophy and the fœtal weight. It has been shown by Baird and Faquhar (1962) that there is an increased insulin-like activity in the plasma of the newborn baby of the diabetic mother. An increase in the fœtal plasma insulin occurs if maternal hyperglycæmia is produced by the intravenous administration of glucose to the mother shortly before her delivery (Milner, 1964). Stimmler *et al.* (1964) demonstrated elevated plasma insulin levels in the newborn babies of diabetic mothers and they found that this increased plasma insulin level persisted for some hours after birth. However, the plasma insulin level showed no direct relationship to maternal blood sugar levels, indicating a factor additional to maternal and fœtal hyperglycæmia. Osler (1960) has demonstrated that the overweight baby of the diabetic mother is overweight because of increased fat. There is no increased total water content of the baby, although there is increased skeletal growth and organ size. All the organs of the body were heavier when compared with fœti of non-diabetic mothers of similar gestational age (Cardell, 1953). If therefore, as seems likely, the anabolic and lipogenic effects of fœtal hyperinsulinism are the immediate cause of fœtal macrosomia, the question arises concerning the cause of the hyperinsulinism. Islet tissue hypertrophy in the baby might well result from one or indeed all of the four following factors:

1. Maternal hyperglycæmia.
2. Increased maternal pituitary growth hormone (diabetogenic factor).
3. Increased maternal adrenal glucocorticoids.
4. The action of the insulin antagonist.

Maternal Hyperglycæmia

It is now well established that in the uncontrolled diabetic woman the fœtus tends to weigh more than in the well-controlled woman (Lawrence and Oakley, 1943; Peel, 1963). Furthermore, it has been shown that by the very careful control of the diabetes, whereby relatively normo-glycæmia is maintained throughout pregnancy, fœtal weight can be reduced (Peel, 1963) (Table 34). However, the

Table 34

FŒTAL BIRTH AND PLACENTAL WEIGHTS IN TWO SERIES

Years 1949–53	No. of Cases	Maturity (days)	Mean Birth Weight	Mean Placental Weight	Placentæ Over 2 lb.
1949–53	125	249	7 lb. 5 oz.	1 lb. 13 oz.	34
			Range: 2 lb. 5 oz. to 10 lb. 7 oz.	Range: 14 oz. to 3 lb. 8 oz.	
1958–61	127	260	7 lb. Range: 2 lb. 12 oz. to 9 lb. 8 oz.	1 lb. 7 oz. Range: 10 oz. to 2 lb. 10 oz.	4

reduction by this means still does not bring fœtal weight down to that of the baby of the non-diabetic. There is no positive evidence that maternal hyperglycæmia is present in the pre-diabetic phase. If maternal and fœtal hyperglycæmia were the sole cause of fœtal macrosomia, one would expect that, in the pre-diabetic phase, the nearer the patient came to the development of clinical diabetes, the larger would be the fœtal weights of any babies born during that period. In fact, the mean maternal blood sugar does not mount gradually in succeeding pre-diabetic pregnancies up to the time of the development of clinical diabetes, and grossly overweight babies may be born as long as 20 or 30 years before the onset of clinical diabetes, at a time when there is no reason to suppose that maternal hyperglycæmia exists. Oakley and Peel (1949) found that the nearer the patient came to established clinical diabetes the percentage of overweight babies became smaller rather than larger. Similar observations in a series of 50 multiparous patients under my care are shown in Table 35. The incidence of overweight babies in the

Table 35

RECENT (UNDER 5 YEARS) PRE-DIABETIC PREGNANCIES
IN 50 MULTIPAROUS PREGNANT DIABETICS

No. of Patients	Pre-diabetic Pregnancies	S.B.		Neonatal Deaths		Perinatal Loss		Babies Over 10 lb.	
		No.	%	No.	%	No.	%	No.	%
50	92	22	24	8	8·7	30	32·7	7	8

5-year period before the onset of clinical diabetes is far lower than the overall incidence of overweight babies in the whole pre-diabetic phase (27% Oakley and Peel, 1949). There must therefore be a factor additional to simple hyperglycæmia. A patient recently under my care gave birth to binovular twins, both babies being subjected to an identical maternal environment throughout pregnancy. One baby was the typical overweight, fat child weighing $9\frac{1}{2}$ lb. (4·25 kg.) at 37 weeks. The other was a normal baby weighing 5 lb. (2·25 kg.) which showed none of the clinical features of the typical newborn baby of the diabetic mother.

Maternal Growth Hormone

Ever since Young (1937) first showed that permanent diabetes could be induced in dogs by the administration of pituitary extract rich in growth hormone, the exact place the pituitary growth hormone plays in the ætiology of clinical diabetes and of the phenomena of diabetic pregnancy has remained uncertain. Erlich and Randall (1961) have shown elevated serum growth hormone concentration in obese patients suffering from diabetes. They similarly found elevated levels in 5 pregnant diabetics. It is at present accepted by experts working in this field that the determination of serum growth hormone during pregnancy is still technically suspect, and until a completely reliable method for its determination can be established, the exact role which it plays as a causative factor of fœtal macrosomia, as well as of clinical diabetes, must remain a matter of speculation.

Maternal Adrenal Glucocorticoids

There is an increased output of glucocorticoids during pregnancy, and the Cushingoid appearance of the baby of the diabetic mother has led to the suggestion that these typical changes are due to this factor (Hoet, 1954). However, although the baby has a superficial

resemblance to the adult suffering from Cushing's disease, the fact that there is no appreciable increase in total body water or salt, makes it unlikely that increased maternal adrenal glucocorticoids could be directly responsible for fœtal macrosomia. Plasma levels and the urinary excretion levels of both cortisol and aldosterone are increased in pregnant diabetics (Rinsler and Rigby, 1957). The increase in adreno-cortical activity could be responsible for the increased insulin needs of the mother during pregnancy, and also for the electrolyte changes that occur in the fœtus to which reference will be made later.

Insulin Antagonists

There are three types of anti-insulin factor in the human:

1. The insulinase enzyme system responsible for the relatively short life span of insulin *in vivo*.
2. Insulin antibodies which are iatrogenic and develop as the result of administered insulin.
3. True insulin antagonists.

Insulin antagonism was demonstrated in the albumin fraction of the plasma proteins by Vallance Owen *et al.* (1958). It is apparently dependent upon the pituitary-adrenal system. It appears to oppose the action of insulin in muscle but not its lipogenetic effect (Pyke and Please, 1957). High levels of insulin antagonists have been found in the serum of obese diabetics and in pre-diabetics (Vallance Owen and Lilley, 1961). Being of low molecular weight it is postulated by them that the antagonist crosses the placenta into the fœtal circulation, and is an added factor responsible for fœtal hyperinsulinism, even in the presence of normo-glycæmia. The insulin antagonist could explain the primary abnormality in diabetes, and Vallance Owen has produced much evidence that it is genetically transmitted as a simple dominant factor. The fœtus possessing the insulin antagonist would tend to suffer from hyperinsulinism and to become overweight, whereas a baby not having inherited such an antagonist would not suffer the same metabolic changes. This would explain not only why the baby of the diabetic and the potentially diabetic mother is frequently obese, but also why the patient with the diabetic potential tends to become obese in middle age. She does in fact become obese because she is diabetic, and not diabetic because she is obese. However, in view of the dependence of the insulin antagonist on the pituitary-adrenal system, it may well

be that all four of the above-mentioned factors have an influence upon the development and growth of the fœtus *in utero* both in the diabetic and in the potentially diabetic phase of the mother's life. An interaction of all four factors would explain not only why the babies of the diabetic mothers tend to be overweight, but also why there is such a wide variation since the weight of any individual baby is dependent upon many factors. It is partly associated with its inherent growth impulse—a genetic factor, but also influenced by gestational age, maternal age, parity and maternal nutrition. We are perhaps seeking for an oversimplification of a very complex metabolic process if we try to pinpoint a single causative factor for fœtal macrosomia.

Perinatal Mortality

The perinatal mortality is at best nearly three times the overall figure. I think that, in the present state of our knowledge, it may help to clarify our ideas and to emphasize points connected with the management of patients suffering from clinical diabetes, if we attempt to divide the perinatal mortality into two categories—the avoidable and the unavoidable. There is inevitably some degree of overlap in individual cases where it is difficult to know exactly into which category one should place the perinatal death. Lawrence and Oakley (1943) were among the first to demonstrate the importance of good diabetic control in relation to perinatal mortality. This fact has been confirmed by many authors since, but especially by Pederson and Brandstrup (1956). More recently our own experiences at King's College Hospital have shown that rigid control of the diabetic state, the avoidance of ketosis, and the preservation of a relatively

Table 36

FŒTAL MORTALITY IN 693 VIABLE PREGNANCIES

Years	No. of Cases	Stillbirths No.	%	Neonatal Deaths No.	%	Total Fœtal Loss No.	%
Before 1941	49	11	22·4	5	10·2	16	32·6
1941–1948	141	16	11·2	20	14·2	36	25·4
1949–1952	102	9	8·8	17	16·7	26	25·5
1953–1958	201	27	13·4	21	10·4	48	23·8
1959–1964	200	9	4·5	14	7·0	23	11·5

normal blood sugar level throughout the last 2 months of pregnancy, will reduce fœtal weight and lower perinatal mortality from approximately 25% to about 10% (Table 36). This reduction of 15% represents the avoidable perinatal mortality. Although a small series is reported from time to time in the literature recording perinatal mortalities of considerably less than 10%, it is the universal experience in all clinics dealing with large numbers of patients, that it is extremely difficult, if not impossible, to lower the perinatal mortality below 10%. This figure is more than three times the overall perinatal loss and is what I refer to as the unavoidable mortality. There are certain known factors which do contribute to perinatal mortality in addition to control of blood sugar level.

Chronic Vascular and Renal Disease

The long-standing diabetic is very prone to develop hypertension and/or albuminuria. White (1952) emphasized the importance of these complications and laid particular stress upon them in relation to perinatal loss. At King's College Hospital approximately 25% of all our diabetic patients have a pre-existing hypertension in excess of 130/90 mm. Hg, and many of these have had traces of albumin in the urine before pregnancy. Chronic renal and vascular disease are known to cause placental infarction, fœtal hypoxia, premature labour and, in severe cases, intra-uterine death. Inevitably they must contribute to the unavoidable fœtal loss.

Pre-eclamptic Toxæmia

The incidence of pre-eclamptic toxæmia is usually stated in the literature to be increased in diabetic pregnancy. What is seldom stated, however, is how many cases are primary and how many are superimposed upon a pre-existing hypertension. Consequently the literature gives an incidence which varies from 8% (Peel, 1956) up to 46% (Given et al., 1950), which reflects the variation in the standards of diagnosis of pre-eclamptic toxæmia as well as its positive incidence. Prolonged bed rest in the last 3 months of pregnancy reduces the risk of pre-eclamptic toxæmia becoming superimposed upon hypertension, and it may well have an influence upon the development of primary pre-eclampsia. To this extent, therefore, a portion of the fœtal loss associated with pre-eclamptic toxæmia is avoidable, but in many cases it remains outside the realms of avoidability.

Congenital Abnormalities

It is generally stated that congenital abnormalities are more frequent in the babies of diabetic mothers. White (1952) gave an incidence of 14%, but at King's College Hospital our incidence was 6·3% in 1949. These figures have little comparative meaning as there is no generally accepted definition of what constitutes a congenital abnormality. Congenital abnormalities may remain undetected and become apparent only as the child grows up. Long term follow-up therefore is necessary to obtain accurate figures. Such a long term study is at present being undertaken at King's College Hospital. Hagbard (1958) reported the results of follow-up during the first year of life and recorded an incidence of 7·6% in 514 children of diabetic mothers. He also found that 2·9% were lethal abnormalities which, he maintains, is three times the rate of an average series of non-diabetics. Pederson *et al.* (1964) provide the most recent survey on this subject, and they found an overall incidence of 6·4% in a series of 853 babies, which compares very closely with the incidence given from King's College Hospital in 1949. Their control figure was 2·1%. In a series of 82 infants coming to necropsy they found an incidence of 19·5%, compared with 6·6% in a control group. They emphasized the frequency of gross limb deformities and congenital heart lesions, and claim that the incidence is much higher in the children of the long-standing diabetic mother suffering from vascular and renal complications. Our experience at King's College Hospital confirms the frequency of limb and cardiac deformities, but we have not so far been able to confirm the association with chronic vascular complications. Nor is it our experience that congenital abnormalities constitute so high a proportion of the primary cause of fœtal mortality. In fact, in a study of postmortem findings in a series of perinatal deaths, Cardell (1953) found no difference between the infants of diabetic and non-diabetic mothers. The causative factor in these congenital anomalies is quite unknown. Hyperinsulinism, hypoglycæmia, hypoinsulinism, hyperglycæmia and oral hypoglycæmic agents have all been implicated as possible teratogenic agents, but so far none of these theories has been substantiated. Sterne and Lavreiville (1963) recently reported a series of 36 diabetic mothers treated with oral hypoglycæmic agents and no resulting congenital abnormalities, whereas in a series of 70 pregnancies treated by insulin 3 malformations occurred. These numbers are not large enough for legitimate conclusions, but there is at present no evidence that oral hypoglycæmic agents have a teratogenic influence. The consensus of

opinion, however, is that congenital anomalies are higher in diabetic pregnancy.

Hydramnios

In diabetic pregnancy the incidence of hydramnios is increased and the associated perinatal mortality rises (42·2%) (Oakley and Peel, 1949). We have shown that there is no relationship between maternal blood sugar levels, the sugar content of the liquor amnii, the fœtal blood sugar levels and hydramnios. At the same time it has been our recent experience that the amount of liquor amnii can be reduced by the regime of hospitalization and bed rest as well as by rigid diabetic control. We regard the failure to reduce liquor volume (as assessed by clinical means) or a positive increase in hydramnios, as a bad prognostic indication of fœtal survival. Liquor volume can only be assessed critically at Cæsarean section or induction, so we have carried out a series of more accurate determinations shortly before delivery. We have used the Coomassie Blue technique described by Elliot and Inman (1961). In a small series of 26 patients in the 38th week of pregnancy the liquor volume fell mostly within the normal range of 800 ml. to 1,200 ml. reported by Elliot and Inman (1961). All cases, however, were well controlled diabetics, hospitalized from the 32nd week of pregnancy. This supports our clinical impression that liquor volume can also be reduced by strict diabetic control, and that hydramnios is a serious sign when assessing fœtal prognosis. It is partly preventable by good diabetic control, but there is also an unavoidable and unknown element.

Any or all of the above factors may cause intra-uterine death or lead to early neonatal death following premature delivery, whether spontaneous or induced. Birth injury, particularly associated with shoulder dystocia, or neonatal infection, may contribute to perinatal loss, and both should be considered within the avoidable group. Early neonatal death is mainly due to the respiratory distress syndrome, and not to infection, birth injury or congenital abnormalities. It is not certain whether the baby of the diabetic mother is more prone to respiratory distress syndrome than that of the non-diabetic born at a similar maturity, but evidence will be presented below to suggest that this is in fact so. There is no doubt that a high incidence of the respiratory distress syndrome is associated with prematurity, and that the nearer the patient is to term, the lower is the incidence. With improved methods of treatment

for the respiratory distress syndrome in the neonate, the death rate has been reduced considerably, but has not yet been completely eliminated because of both avoidable and unavoidable factors.

Perinatal mortality of approximately 10% is still three times the overall figure, but it is unlikely that this will be lowered much further until we can determine the essential cause of intra-uterine fœtal death and adopt appropriate preventive measures.

In a series of investigations carried out at King's College Hospital involving the determination of fœtal hæmoglobin levels, the oxygen saturation of the umbilical cord blood, the uterine blood flow and placental bed biopsies, no convincing evidence was found that placental insufficiency exists in diabetic pregnancy (Peel, 1962). At the present time it is not possible to lay the blame for intra-uterine fœtal death primarily at placental level. Intra-uterine fœtal death is not more liable to occur when the baby is smaller than normal, as would be expected if placental insufficiency and hypoxia were the primary cause of death. In fact we have shown that perinatal mortality is in no way related to fœtal weight, except in relation to maturity (Table 37). Naturally a higher percentage of very small premature babies will die in the neonatal period, but intra-uterine fœtal death occurs with equal frequency in babies small, normal or large.

Table 37

RELATION OF FŒTAL WEIGHT AND MATURITY TO
PERINATAL MORTALITY 1958–64

	Total	No. over 7 lb.	Maturity (mean) in Days	No. under 7 lb.	Maturity (mean) in Days
Stillbirths	12	7	257	5	230
Neonatal deaths	17	8	259	9	241
Perinatal loss	29	15		14	

Another point to emphasize is the frequency with which perinatal loss is repeated in succeeding pregnancies. A high percentage of diabetic mothers have a series of pregnancies with minimal complications and no perinatal mortality. In others perinatal loss tends to be repeated in succeeding pregnancies. I have found that patients who have lost two babies in spite of good management and satisfactory diabetic control have at least a 50% chance of having a

third stillborn baby. A patient recently under our care had a series of 10 pregnancies with only two living children. The last three pregnancies all ended in intra-uterine fœtal death between the 34th and the 36th weeks of pregnancy, in spite of excellent diabetic control. There is an unknown factor present in this group of patients, and the resulting perinatal loss is therefore unavoidable.

The Effects of Pregnancy on Diabetes (Long Term)

There is ample evidence to suggest that repeated pregnancies occurring in the potential diabetic lead to the development of manifest clinical diabetes after the age of 45, and, in many instances, much earlier. It is also common experience that transient gestational diabetes recurs in succeeding pregnancies, and is followed by manifest diabetes in nearly all instances. Hagbard and Svanborg (1960) reported 37 such patients, all of whom became diabetic in the long-term follow-up. This corresponds with our own experience. Surprisingly, there is as yet no clear evidence that the established diabetic is made permanently worse by pregnancy, if one judges worsening of the disease in terms of insulin need. Hagbard (1956) followed 250 patients for 6 months after pregnancy and found that the insulin requirement was the same in 65%, increased in 18%, decreased in 17%. Whenever a modification occurred the relative change was slight and never exceeded 12 units per day. However, in considering the long-term effects, it is not only the insulin requirement that must be assessed, but also the complications of diabetes— hypertension, nephropathy and retinopathy. Severe toxæmia or greatly increased hypertension during pregnancy usually accelerate the subsequent progress of both the hypertension and the nephropathy. The effect of pregnancy upon retinopathy is most difficult to judge, because in the past it has usually been regarded as a contraindication to pregnancy. Reports, therefore, have little statistical value but retinopathy appears to progress during pregnancy. Hagbard reported no progression of simple retinopathy in 11 patients, although the lesion advanced in one out of three patients with proliferative retinopathy.

Contraindications to Pregnancy

It is becoming more frequent for diabetic patients to seek medical advice before embarking on a pregnancy. This is wholly desirable, because there is much evidence that good control early in pregnancy avoids many of the complications that may occur in both early and

late pregnancy. At the same time it is desirable because pregnancy may be prevented in a patient in whom it is contraindicated, and the necessity to advise termination can therefore be avoided. However, there are still instances where pregnancy occurs because the patient has not sought prior advice and yet a pregnancy may be deemed undesirable or positively dangerous. The need for termination can only be judged in each individual case, and as in other conditions where termination of pregnancy is discussed, ethical and moral considerations may influence either the patient or her medical adviser. Aside, however, from these latter considerations, there are several factors which should always be carefully considered as possible contraindications to pregnancy:

1. *The Genetic Factor*, particularly the presence of a family history of diabetes on both the maternal and paternal sides.

2. *Vascular and Renal Complications*. Oppe *et al.* (1957) reported 45 patients falling within Priscilla White's classification Class F, in whom only 45% of the babies survived. Mention has already been made of the increased maternal risks of pregnancy in diabetics with vascular, renal and retinal complications.

3. *Family Size*. High multiparity is undesirable for the diabetic mother, not only because the added stress of caring for a large family may seriously interfere with her ability to care for her own disease, but also because of the diabetogenic effects of multiparity.

4. *Duration of Diabetes*. The main weight of evidence is that duration of diabetes in the absence of chronic vascular and renal complications does not influence the perinatal mortality. Experience shows, however, that the very long-standing diabetic (over 25 years) has a higher incidence of maternal complications during the course of pregnancy. The duration of the disease must, therefore, be taken into consideration whenever the question of termination of pregnancy is under discussion.

5. *Habitual Fœtal Loss*. I have already made reference to habitual unavoidable perinatal mortality in certain patients. In the last 28 multiparous diabetic women at King's College Hospital who have had perinatal loss, no less than 22 had previously experienced one or more obstetric failure, in spite of good diabetic and obstetric care. One recent patient had experienced 10 pregnancies and achieved only 2 live babies. The last 3 pregnancies had resulted in intra-uterine fœtal death before the 36th week, 2 of these being associated with gross congenital anomalies. The chance of a successful pregnancy with such a history is very remote and would, I think, justify termination.

6. *The Co-operation of the Patient.* The successful outcome of pregnancy in any diabetic woman is essentially dependent upon her willingness to co-operate throughout the entire pregnancy.

7. *The Availability of Medical Care.* This is a factor not important in this country, but it is one which has to be occasionally considered in patients who are allowed to travel abroad or who take up residence in the more remote parts of the world where expert medical care is not readily available.

If, after full consideration and consultation, termination is deemed desirable on medical grounds, it is nearly always advisable to carry out sterilization at the same time. Alternatively, if at the conclusion of a full-time pregnancy, whether successful or not, further pregnancies are definitely contraindicated, sterilization can be offered and carried out early in the puerperium. This is the most satisfactory way of ensuring permanent sterility and relieves the patient of much anxiety.

Antenatal Care in the Established Diabetic

The antenatal care of the diabetic patient should be shared by the obstetrician and the physician responsible for the management of her diabetes. The closest possible co-operation between the two is essential if good results are to be obtained. Although most of the more serious complications of diabetic pregnancy occur in the last trimester, there is much evidence to show that the earlier in pregnancy the patient comes under the control of obstetrician and physician, the better are the results (Pederson and Brandstrup, 1956). Davidson (1963) showed that in terms of foetal survival, results were better when the patient was brought under control early rather than late in the pregnancy. This too has been my own experience.

There are three main reasons why control of the diabetes becomes more difficult during pregnancy, and furthermore as pregnancy progresses the difficulties increase.

1. The effects of vomiting (particularly liable to occur in the first trimester).
2. The marked lowering of the renal threshold, which usually manifests itself during the second trimester.
3. The increase in insulin needs as pregnancy progresses.

Excessive vomiting in the early weeks of pregnancy requires that the patient be admitted to hospital immediately. Ketosis is liable to develop as the result of vomiting in any pregnant woman. In the

diabetic woman this is infinitely more serious and develops even earlier. In the absence of prompt treatment the possibility of damage to fœtal nutrition cannot be excluded and abortion is more likely to occur. In the second trimester when the renal threshold goes down, the diabetes becomes particularly liable to instability and ketosis develops rapidly. Lowering of the renal threshold makes urine testing a totally unacceptable yardstick whereby to judge control of the diabetes. Urine testing for ketone bodies is essential, but the diabetic control can only be satisfactorily gauged by blood sugar estimations.

Medical Care of the Diabetes

Most patients are the young insulin-dependent type of diabetic who are already taking insulin when pregnancy starts. Frequently they are taking a single dose of long-acting insulin, and in some patients it may not be necessary to change this regime immediately. However, it is usually desirable, soon after the diagnosis of pregnancy, that the patient be changed to morning and evening doses of insulin, which will have to be increased as the pregnancy progresses. In order to maintain stable and reasonably low blood sugar levels, soluble insulin by itself is not sufficient. It has been our aim to maintain the blood sugar consistently below 160 mg./100 ml. (absolute glucose) during the last 8 weeks of pregnancy. In the earlier months such strict control is not possible because the patient can be seen only during the routine periodic antenatal visits. It is often desirable to admit the patient about mid-pregnancy for a few days for re-assessment, particularly if there is a tendency to develop ketosis. At this time it is usually necessary to introduce, in addition to soluble insulin, one of the long-acting preparations. This can be done in one of two ways:

1. Prolonged hypoglycæmic action to carry the patient through the night may be obtained by adding a small dose of protomine zinc insulin (4 to 16 units) to the evening dose, given about 3.30 p.m.

2. An alternative method which has been adopted more recently is to add an appropriate dose of isophane insulin to both the morning and the evening injections of the soluble preparation. They are given before breakfast and before the evening meal. Diet is not reduced unless weight increase exceeds the normal. The normal carbohydrate intake is maintained between 180 g. and 200 g. a day and it is seldom wise to reduce it below

150 g. It is important to remember that, if the renal threshold is particularly low, ketosis may develop because the patient is losing so much glucose in the urine. She may, therefore, have heavy glycosuria plus ketosis, suggesting hyperglycæmia with impending coma. Blood sugar estimations in these cases are often found to be normal or even low; therefore it is advisable to increase the carbohydrate intake by giving a tablespoonful of cane sugar added to each of the three main meals.

Oral Hypoglycæmic Agents

Sometimes a patient is referred, with pregnancy well established, who has been maintained prior to pregnancy on oral hypoglycæmic agents, and has continued their use during the first few months of pregnancy. The two oral hypoglycæmic agents most frequently employed are both sulphonylureas:

1. Tolbutamide.
2. Chlorpropamide.

Patients whose diabetes can be well controlled with these agents are usually aged 35 or more, and they are frequently obese with mild diabetes. If they can be controlled adequately with these drugs, there is no necessity to change immediately to insulin. The evidence that they may produce congenital anomalies in the baby is at present unfounded, but in any case they would exert any such influence in the early weeks of pregnancy. However, if the diabetic condition becomes unstable and difficult to control, there should be no hesitation in changing from the oral preparation to insulin.

Infections

During the first and second trimesters of pregnancy there are no special features, but there are two common complications much more likely to be encountered in the diabetic woman.

1. Pyelonephritis.
2. Vulvo-vaginal infections.

Both these conditions follow the same clinical course as that which is encountered in the non-diabetic, and fundamentally require the same treatment. Nearly all cases of vulvo-vaginitis are associated with monilial infection, but of course bacterial infection may occur and also infestation with *Trichomonas vaginalis*. Once having occurred, they are particularly liable to recur. Both conditions also have the tendency to interfere temporarily with the stability of the

diabetic control. Treatment in no way differs from that undertaken in the non-diabetic, but in both disorders it is usually necessary to continue treatment either intermittently or continuously until the end of the pregnancy. It is an interesting observation that renal glycosuria in the non-diabetic is much less liable to be associated with monilial vulvo-vaginitis and pruritus vulvæ.

Management During the Last Eight Weeks of Pregnancy

For some years it has been our practice at King's College Hospital to admit all patients to hospital at some time between the 30th and the 32nd week of pregnancy and to keep them resting in bed until they are delivered. This has the advantage of making diabetic control easier and more complete. At the same time bed rest improves uterine blood flow and placental function, tends to reduce blood pressure and in those suffering from mild hypertension it minimizes the tendency to fluid retention. Sedatives such as phenobarbitone or amytal are frequently given to patients suffering from hypertension, but the indications and contraindications for hypotensive drugs and diuretics are precisely the same as in the non-diabetic. Some authorities claim good results without hospitalization (Drury, 1962). The main objections to hospitalization are social and economic. Normally pregnancy is not interfered with until towards the end of the 37th week.

Termination before the end of the 37th week is undertaken if any of the following conditions develop:

1. *Extreme Difficulty in the Control of the Diabetes.* This is sometimes an indication of impending intra-uterine fœtal death, and if the baby is reasonably mature it is safer to terminate a week or so earlier.
2. *Sudden Drop in the Insulin Requirement.* This frequently heralds the onset of intra-uterine fœtal death, but not always, and occasionally it occurs for no apparent reason and without any ill-effects to the fœtus. Again, earlier termination should only be carried out if the pregnancy is mature enough to stand a reasonable chance of fœtal survival.
3. *The Development of Severe Hydramnios.* An X-ray should always be taken in order to determine the presence or absence of any severe skeletal congenital anomaly.
4. *The Presence of a Very Large Baby*, particularly if there is a history of a previous intra-uterine fœtal death. There is often an associated hydramnios.

5. *Increasing Hypertension* or progressive pre-eclamptic toxæmia.
6. *Previous Intra-uterine Fœtal Death* in spite of good control. In these circumstances I tend to terminate the pregnancy about 1 week earlier than the date at which intra-uterine fœtal death occurred in the previous pregnancy. This is important in those instances of recurrent intra-uterine fœtal death, but even so an appreciable number of the babies succumb in the early neonatal period if the pregnancy has to be terminated before the 37th week.

At the present time there is no completely reliable method of diagnosing impending intra-uterine fœtal death. Ever since Smith *et al.* (1937) showed that there was an elevated serum chorionic gonadotrophin level in many diabetic pregnancies and an associated fall in the level of œstrogens and progesterone, interest has been taken in the possible role that hormones play in regard to diabetic pregnancy and its complications. No convincing evidence has ever been produced to show that complications can be reduced and perinatal mortality improved solely by the administration of œstrogens and progesterone, although their administration does lead to a fall in the level of serum chorionic gonadotrophin. Hormone therapy has therefore been almost universally abandoned, but much work has been carried out in regard to hormone assays in blood and urine.

Attempts have been made to arrive at a fœtal prognosis from the results of estimations of pregnanediol excreted in the urine, and more recently of œstriol. The assay of pregnanediol in the urine has been shown by Scott Russell *et al.* (1957) and many others to be a valuable guide to placental function in conditions such as hypertension and toxæmia, but to be no reliable prognostic guide in the individual cases in diabetes. During a trial of hormone therapy carried out in several centres in this country and reported by the Medical Research Council in 1955, it was shown that a drop in the urinary pregnanediol did occur at about the 32nd week of pregnancy in those patients in whom ultimate intra-uterine fœtal death occurred. There was, however, such a wide variation from day to day and from patient to patient in the urinary excretion levels that pregnanediol assays have now been largely abandoned as a prognostic test for impending intra-uterine fœtal death in diabetic pregnancy Clayton, (1956). More recently, several series of cases have been published of œstriol assays in diabetic pregnancy (Hobkirk *et al.*, 1960; Frandsen, 1962; Ten Berge, 1960; and others). Taylor *et al.* (1961) found no abnormalities in œstriol excretion in diabetic

and non-diabetic pregnant women. Roy and Kerr (1964) found that the blood œstrogens were within normal limits, although the mean values were very slightly lower in the diabetic compared with non-diabetic group. All authorities, however, have shown that a very low value of œstriol excretion occurs at the time of intra-uterine fœtal death and sometimes for a short period before. The mean level of œstriol excretion in normal pregnancy rises steadily and over 12 mg. are normally excreted every 24 hours in the last trimester (Banerjea, 1962). A value below 4 mg./24 hr. is indicative of impending fœtal death. Between 4 mg. and 12 mg. is regarded as borderline. Whilst these figures can be accepted as factual, it is far from established that œstriol excretion studies will prove an entirely reliable criterion upon which to base the timing for the termination of pregnancy. Much work, currently in progress, is attempting to assess the prognostic value of urinary œstriol assays in diabetic pregnancies. It is apparent that there is a very wide variation in the excretion rates from day to day. Reference to Fig. 39 illustrates how difficult it is always to base one's action upon the results of urinary œstriol assays. In one patient the urinary excretion of œstriol was at an extremely low level, below 4 mg./24 hr. as early as the 31st week. In another case the figure was well over 12 mg./24 hr. a few days before intra-uterine fœtal death suddenly occurred when the œstriol excretion dropped dramatically. In order to use œstriol assays for prognostic purposes it is necessary to carry out
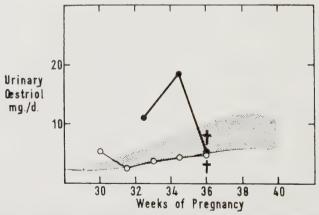
Fig. 39. Showing variation in urinary oestriol excretion levels at different stages of pregnancy.

the test daily in the few weeks immediately preceding the normal time for termination. Until an easy, quick and reliable method is available such a technique is impractical in most units. There is always the danger that if delivery is accomplished too early, on the evidence of a low œstriol excretion the baby may die in the neonatal period. Perinatal mortality is thereby merely transferred from the column of intra-uterine fœtal death to that of early neonatal death. No series of cases has yet been published in which the routine use of œstriol assays has been successful in lowering perinatal mortality compared with any other series that has been managed without this additional diagnostic aid.

Another technique currently being investigated is the change in the cellular pattern of the vaginal smear. Changes in vaginal cytology have been demonstrated in relation to threatened abortion, impending intra-uterine fœtal death and postmaturity (Wood *et al.*, 1961). MacRae (1964), however, found no consistent changes in a small series of diabetic patients so investigated. Much work remains to be done in both these fields of investigation before their true value or significance can be appreciated and their exact place as diagnostic and prognostic weapons assessed.

In determining the correct moment to terminate pregnancy it is important to individualize every patient. Pregnancy should never be allowed to continue beyond the end of the 37th week (266 days), but earlier termination will be determined by a consideration of all the circumstances concerned in the past history and the present condition.

Mode of Delivery

The pregnancy may be terminated by Cæsarean section or labour may be induced. Opinions vary about the relative place of these two alternative methods. My own experience is that approximately 50 % of patients can be delivered safely by the vaginal route following induction, but that Cæsarean section is advisable in the other half. Tables 38 and 39 show the indications for induction and Cæsarean

Table 38

INDICATIONS FOR INDUCTION OF LABOUR IN DIABETICS

1. Primigravida under 30 obstetrically normal.
2. Multipara with good obstetric history.
3. Maturity—into 38th week.
4. Diabetes well controlled.
5. Baby under 8 lb.
6. Absence of hydramnios.
7. After I.U.D.

Table 39

1. Primigravida over 30 years.
2. Multipara with bad obstetric history.
3. Diabetes difficult to control.
4. Obstetric complications.
5. Large baby—over 8 lb.
6. Vulval œdema and vulvo-vaginitis.
7. Marked Hydramnios (fœtus normal).

section that are followed at King's College Hospital. Induction of labour is carried out invariably by low rupture of the membranes. Because there is frequently a long induction/delivery interval following premature artificial rupture of the membranes, I now routinely set up an oxytocin drip when artificial rupture of the membranes is performed. By this means I have found that a much higher percentage of patients go into labour within 12 hours, and the necessity for Cæsarean section following failure of induction is thereby reduced. Because of the great difficulty of controlling the patient's diabetic state even by continuous intravenous therapy throughout the course of a very long labour, it has become our custom to carry out Cæsarean section if the patient is not in established labour within 48 hours following induction, or if active labour persists for more than 24 hours without normal progress. In regard to vaginal delivery, there are two points that require special reference:

1. The grave risk of shoulder dystocia if vaginal delivery is attempted when the baby is too large. I have seen several stillbirths due to shoulder dystocia even after easy delivery of the fœtal head.
2. The unhealthy state of the vulval and vaginal tissues in patients who have had long-standing vulvo-vaginal infections and pruritis. The tissues lacerate easily and heal badly.

The presence or addition of any marked vulval œdema is, in my view, a clear indication to avoid vaginal delivery.

If elective Cæsarean section is to be carried out the patient should be given nothing to eat or drink within 4 hours of operation. If she has had food or drink within that period, the stomach should be washed out. The aim should be to send the patient to the operating theatre with a blood sugar as near normal as possible, and the urine free of ketone bodies. At the time of induction of anæsthesia, an intravenous injection of 20 ml. of 50% glucose is given, or

alternatively an intravenous glucose drip may be set up. It is important to remember that there is usually a dramatic drop in insulin requirement following delivery. No post-operative insulin should be given until a blood sugar has been estimated, and upon return to the ward the patient should be put on a 4-hourly emergency regime.

The Newborn Baby

Fortunately in many cases, the newborn baby of the diabetic mother behaves quite normally and requires no special care other than that of any baby 2 or 3 weeks premature. Many of the babies, however, have an abnormal and very typical physical appearance, and also behave in very characteristic ways during the early neonatal period. Typically the baby is overweight, grossly fat, and the colour of the skin is much redder than normal. It has been described as "Cushingoid" and there is very frequently an excessive crop of dark hair on the head. At birth the baby is not actually œdematous, but becomes so very rapidly, and when seen a few hours after birth, is much more plethoric and congested in appearance than at the moment of birth. During the first 12 hours of life, these babies have a particular liability to develop the respiratory distress syndrome. The incidence of this disorder is greatly reduced if the diabetes is well controlled during the antenatal period, and if the time of delivery can be safely delayed until the end of the 37th week. Respiratory distress syndrome is much more common in babies delivered earlier than this. Typically, respirations are grunting in type and increased in rate, being associated with marked rib retraction. Frequent cyanotic attacks occur, associated with quite long periods of apnœa. Tachycardia is invariable, muscle tone is poor and the baby shows an extreme irritability whenever it is disturbed. Usually diminished breath sounds and numerous rales are detected in the lungs. In the terminal stages jaundice, paralytic ileus and great abdominal distention may manifest themselves.

The respiratory distress syndrome has been shown to be associated with the rapid development of a respiratory acidosis, which is followed later by metabolic acidosis. That such an acidosis is more frequent in the babies of diabetic mothers, was first suggested by Graham and Lowry (1953). They showed that in the babies of diabetic mothers, the average pH was 7·2, compared with 7·33 in a series of normals. In the babies of diabetic mothers the P_{CO_2} was 49 mm. Hg, compared with 35 mm. Hg. At 4 hours the pH was

7·35, compared with pH 7·4, and the P_{CO_2} 44 mm. Hg, compared with 30 mm. Hg. Similar figures were found by Kaiser and Goodlin (1959). In their series the diabetic baby had a pH of 7·25, compared with a pH of 7·34 in the normal. The P_{CO_2} was 49·7 mm. Hg, compared with 41·6 mm. Hg. Results from a series of 61 babies investigated by Seligman (1962) at King's College Hospital showed pH values at 20 minutes after birth of 7·22, compared with 7·3 in controls, and a P_{CO_2} of 53·5 mm. Hg, compared with 43·1 mm. Hg in the control group (Table 40). All these figures are so close that

Table 40

61 BABIES OF DIABETIC MOTHERS
MEAN AND STANDARD DEVIATION VALUES OF ACID-BASE MEASUREMENTS

	Apgar 7–10	Apgar 3–6	Apgar 0–2	Total	Controls
P_{CO_2} mm. Hg					
20 minutes	51·4 (16·28)	55·6 (14·11)	58·7 (4·91)	53·5 (15·50)	43·1 (7·71)
3 hours	43·0 (7·29)	43·1 (8·43)	46·7 (5·74)	43·4 (7·49)	37·6 (5·67)
12 hours	39·0 (4·47)	39·1 (4·12)	39·7 (5·16)	39·1 (4·37)	34·3 (4·83)

pH Values Equivalent to Hydrogen Ion Concentrations					
20 minutes	7·235	7·215	7·19	7·225	7·30
3 hours	7·30	7·285	7·245	7·29	7·34
12 hours	7·375	7·355	7·36	7·37	7·40

they can be accepted as reliable. Following the acidosis, the plasma potassium rises rapidly. If the pH falls below 7·15 or the potassium rises above 9 mg./100 ml. the baby rarely survives. In the respiratory distress syndrome Usher (1959) introduced the method of treatment by means of intravenous sodium bicarbonate with glucose. He showed that, in a series of 35 premature babies treated by this means, the mortality was reduced to 17% compared with a series of controls in which the mortality was 37%. Currently therefore the accepted method of treatment of these babies is as follows:

Firstly, an expert should be present in the theatre or delivery room for adequate resuscitation at the time of birth and the assurance of a completely free airway. Intubation is frequently necessary and should not be delayed if there are any signs of respiratory difficulty. The baby is moved to an Isolette, where adequate humidification can be maintained in order to prevent water loss from the respiratory tract. Oxygen need not be given routinely, but only if cyanotic

attacks develop. Ideally the blood pH and P_{CO_2} should be estimated at birth and again at 3 hours, or sooner if the baby shows signs of developing the respiratory distress syndrome. If this does develop, an intravenous drip should be established through the umbilical vein and a solution of bicarbonate of soda ($8\cdot4\%$) with glucose (15%) given. My own experience in treating the babies of diabetic mothers with respiratory distress syndrome by this method is limited to a small number because the incidence of this disorder has been so greatly reduced during the last few years, that I have not had many babies requiring treatment. However, 3 of the last 4 who have developed severe respiratory distress syndrome have survived following this method of treatment, whereas previously once the disorder became fully established recovery was rare. It is important to emphasize that if treatment is to be carried out successfully, it must be established early. In one of our earlier cases treatment was not started until 12 hours and the baby died in spite of treatment.

Other Causes of Neonatal Death

It was at one time suggested that hypoglycæmia might contribute to early neonatal death. That hypoglycæmia does sometimes occur in these babies is accepted, but it is also common in the babies of non-diabetic mothers and proof is lacking that it is a factual cause of neonatal death. It is extremely dangerous to commence oral feeding too soon. The hazards of hypoglycæmia as understood at the present time do not justify routine intravenous therapy for all babies. Reardon (1959) is an advocate of routine feeding with glucose, but at the present time he has little support from practising clinicians.

Neonatal infections are certainly more common in the babies of diabetic mothers, but fortunately, with modern antibiotic therapy, they rarely prove fatal. Occasionally congenital anomalies, particularly cardiac and rarely renal, account for early neonatal death. More often congenital heart disease does not prove fatal during the first month of life.

Lactation is defective in a very high percentage of diabetic mothers. Premature delivery or Cæsarean section, together with the fact that the baby is frequently lethargic and slow during the first week or 10 days of life, all mitigate against successful breast feeding. However, apart from these adverse influences there is no doubt that defective lactation is one of the characteristics of the syndrome

of diabetes and pre-diabetes. This is probably associated with defective function of the anterior pituitary. Further evidence of such dysfunction is that irregularities in the restoration of normal menstrual function are more common following delivery in diabetic women, than in non-diabetic women. The majority of babies therefore have to be bottle-fed. However, once over the early hazards of respiratory difficulty and the later difficulties with feeding, these babies grow and progress quite normally.

Diabetes and Gynæcology

There are many ways in which the problems of abnormal carbohydrate tolerance and gynæcological disorders have to be considered in the same patient. Clinically the problem presents itself in one of two ways:

1. The problems of management when an established diabetic develops a gynæcological condition requiring surgical treatment.
2. The possible relationship between impaired carbohydrate tolerance and various gynæcological disorders.

Although any gynæcological disorder may occur in an established diabetic, the most frequently encoutered problems can be best considered under the three following headings:

1. Disorders of menstrual function.
2. Vulvo-vaginal infective lesions.
3. Gynæcological conditions requiring surgery—e.g. prolapse.

Precise evidence based on controlled series is lacking concerning the incidence of disorders of menstrual function in established diabetics. Oligomenorrhœa and amenorrhœa are not uncommon, not only in adolescence but also in older women. Poor control of diabetes is often the cause for these temporary disorders of menstruation. Nevertheless there is considerable clinical evidence, and it has certainly been my own experience, that irregularities in the menstrual cycle are more common even in the well-controlled diabetic than in the non-diabetic patient. For example, the frequency with which irregular menstrual cycles complicate the clinical problem of determining the exact date of expected delivery in diabetics, is much more than usual. It is also common to get a very prolonged period of amenorrhœa following delivery. Further, deficient lacta-

tion is well recognized in the puerperium. All these facts suggest that pituitary gonadotrophic function may be partially depressed in the diabetic. Although the excellence of modern diabetic control has reduced infertility to the very minimum, if such impairment of pituitary gondotrophic function is in fact inherent in the diabetic state, there must be some degree of impairment of fertility.

The Relationship Between Menstrual Function and Diabetic Control

In the diabetic patient it is not uncommon to find that insulin requirement increases during the premenstrual phase of the normal menstrual cycle. It is uncertain whether this is associated with changes in hormone production or with the emotional and psychological disturbances so frequently present at this time. The exact causation of the premenstrual tension syndrome is uncertain, but this condition in particular makes the diabetes become unstable and affects the insulin dosage. In my experience hormone therapy is disappointing in correcting this disorder.

Since the introduction of the contraceptive "pill", the question has frequently been raised whether this is harmful to the diabetic. Exact evidence upon which to base opinion in this matter is lacking. A few instances have been reported in which patients on the pill have found that their insulin requirements have increased. Swyer (1962) states that normal glucose tolerance curves have been found in a series of non-diabetic patients whilst taking oral contraceptives. It would seem that if the oral contraceptive acts by depressing the anterior pituitary it should exert no harmful effect upon the diabetic. On the other hand, there is no proof that the oral contraceptive does depress anterior pituitary action, and it has been suggested that it may be effective by reason of direct action on the ovary. In the present state of our knowledge there is no more reason to withhold the pill from a patient suffering from diabetes than from any non-diabetic subject.

Vulvo-Vaginal Infections

Infections of the vulva and vagina are particularly common in diabetics. Typical diabetic vulvitis is well known. Vaginal infection is usually due to persistent or recurrent moniliasis. At the same time these women are more prone to bacterial infections, and infestation with *Trichomonas vaginalis* may occur co-incidentally. Because of the diabetes these vulval lesions are much more difficult

to treat. Frequently when the diabetes is temporarily out of control women complain of pruritus vulvæ without any obvious vaginal infection. Restoration of normal blood sugar levels and elimination of ketosis and glycosuria usually result in improvement of pruritus vulvæ. It is interesting that pruritus and monilial infections are infinitely less common in non-diabetic women suffering from simple renal glycosuria. The patient who has suffered from diabetes for many years tends to develop a state of poor nutrition of the skin because of sclerotic changes in the terminal blood vessels and degenerative changes in both the nerves and the nerve endings. The essential management of monilial and other vulvo-vaginal infections is not materially different from that in the non-diabetic. However, the response is much less dramatic and treatment often has to be prolonged. A very important point to stress is that although the patient is a diabetic, she may develop any of the vulval lesions of a more serious nature such as true leucoplakia or epithelioma. Because the patient is a diabetic, there is sometimes a tendency to overlook the early signs of these disorders. Once diagnosed, they should be treated in exactly the same way as in the non-diabetic.

Conditions requiring Surgery

The established diabetic may develop any gynæcological disorder to which the non-diabetic is also liable. The problem most frequently presents in menopausal patients who may have had diabetes for many years, who may be obese and suffering from hypertension. What should our attitude be towards the increased risks of major surgery in this type of patient? The best considered advice has, until recently, often been against surgery for non-urgent gynæcological disorders such as prolapse. Obviously there will be some patients in whom the vascular and renal complications are so far advanced that major surgery is out of the question. However, it is important to remember another aspect of this problem. The presence of a chronic debilitating condition such as major degrees of prolapse is often associated with chronic vaginitis, discharge and urinary infection which may seriously affect the well-being of the diabetic woman, and actually contribute to the difficulty of managing her diabetes. It is for this reason that only the most severe complications of diabetes, such as gross hypertension or coronary arterial disease should be allowed to preclude surgery. The permanent use of a ring pessary in a post-menopausal diabetic woman is definitely contra-indicated. The presence of a persistent infective local lesion seriously interferes with the control of her diabetes.

Preparation for Surgery

The need for precautionary and preparatory measures prior to operation is part of good surgery, but is doubly important before operation on diabetics. Various points of management can be illustrated if we consider the typical problem of a diabetic woman with severe utero-vaginal prolapse. Often the patient is overweight, and it is advisable that for several weeks or even months she should be on a weight-reducing diet. During this time any tendency there may be to local vulvo-vaginitis should be energetically treated and in the post-menopausal patient the use of œstrogens to improve the nutritional condition of the vaginal and vulval epithelium is extremely valuable. Once she has been admitted and prepared for operation, every endeavour should be made to ensure that the patient goes to the operating theatre with a blood sugar as near normal as possible, and with urine free from ketones. This may often require several days of in-patient care prior to operation. Instability of the diabetes should be regarded as an indication for temporary postponement. The patient should be allowed nothing to eat for at least 4 hours prior to surgery. An intravenous injection of 20 ml. of 50% glucose is given at the time of induction of anæsthesia, and a further 20 ml. at the completion of the operation. On return to the ward the patient is put on a 4-hourly emergency regime, whereby both diet and insulin needs are controlled by blood sugar estimations. If post-operative vomiting becomes serious, it is important that nothing be given by mouth, and intravenous therapy must be undertaken. If an emergency operation has to be performed for such a condition as acute torsion of an ovarian cyst or a ruptured ectopic pregnancy, it is important that the stomach should be emptied by stomach tube prior to the administration of general anæsthesia. Even if the surgeon's preference is against an in-dwelling catheter post-operatively, this is usually advisable in the diabetic patient.

Post-operative Complications

These patients are prone to the more serious complications which may, on occasions, affect any woman following major gynæcological surgery, namely urinary tract infection, wound sepsis, venous thrombosis, pulmonary embolism and coronary artery thrombosis. However undesirable one may regard routine prophylactic antibiotic therapy, there is much to be said in its favour in these patients. Wound healing is less good than normal, and

severe infection may destroy the beneficial effects of the operation. A strong case can be made out for the routine use of anticoagulants after the 3rd post-operative day in the obese diabetic woman over the age of 45.

Apart from gynæcological disorders which occur in the established diabetic, we are frequently confronted with the possibility that impaired carbohydrate tolerance and certain gynæcological conditions may have ætiological association. At puberty and during adolescence, clinical diabetes may first develop probably in association with the phase of rapid growth and increased pituitary activity. The gynæcologist is often consulted by a girl suffering from amenorrhœa or oligomenorrhœa with associated obesity. The need for investigation of carbohydrate tolerance in this type of patient should be emphasized. Abnormal glucose tolerance may be detected, even though the patient is not clinically diabetic. A low calorie diet with restriction of carbohydrate will, frequently, not only restore normal glucose tolerance, but re-establish normal menstrual rhythm. Impaired glucose tolerance may occur in more specific pituitary-endocrine disorders, such as pituitary tumours or Cushing's disease associated with menstrual disorders, but it would not be appropriate to discuss these conditions in the present context.

More often the problems of impaired carbohydrate tolerance present themselves to the gynæcologist at the time of the menopause. The incidence of diabetes begins to rise steeply after the age of 45, and it is difficult to dissociate this fact from the menopause with its associated endocrine changes. During this phase of a woman's life there is a gradual reduction in the output of both œstrogen and progestogen, and this is associated with a rise in gonadotrophin. There is considerable evidence that the age of the menopause is later in women developing the pituitary type of diabetes which is so frequently associated with obesity. Apart, however, from frank diabetes there is much evidence to show that lesser degrees of carbohydrate intolerance are common at this time. The recent diabetic survey undertaken by the College of General Practitioners (1962) showed that in women over the age of 50, no less than 48% had abnormal oral glucose tolerance tests. This survey reached the conclusion that, over the age of 50, the proportion of women showing an abnormal glucose tolerance test is about 10 times greater than was previously supposed. This fact makes it essential that much of the evidence linking carcinoma of the endometrium with diabetes should be re-examined. Crossen and Hobbs (1935) were the first to suggest that there was more than a chance relation-

ship between diabetic women who were nulliparous, obese, who had a late menopause and developed carcinoma of the endometrium. Way (1953) investigating a series of cases of carcinoma of the endometrium found an incidence of established diabetes in 29%, and claimed that a further 43% showed abnormal glucose tolerance curves. A similar pattern was shown more recently by Benjamin (1960) who found an incidence of 52% of abnormal glucose tolerance in a series of patients suffering from carcinoma of the endometrium. However, this author produced an even more startling figure of carbohydrate intolerance in 84% of a series of patients suffering from endometrial hyperplasia. This lends much support to the concept that overactivity of the anterior pituitary for a long period may be of primary importance in prolonging ovarian and menstrual function beyond the normal menopausal age, and in the development of endometrial hyperplasia, initially benign and subsequently malignant. Other authors, however, have not been able to find this striking relationship. Joslin (1952) studying 10,000 patients who developed diabetes postmenopausally, found an incidence of malignant disease of the uterus in only a very small percentage. Louis (1958) examined 124 patients and found only 22% with abnormal glucose tolerance. I have investigated 102 patients at King's College Hospital all suffering from carcinoma of the corpus and found frank diabetes in 11%, and in a further 24% the glucose tolerance curves were either frankly abnormal or became suspicious after the administration of cortisone. However, the incidence of abnormal curves was very nearly the same in a series of control patients of the same age group, and in a series of patients suffering from benign endometrial hyperplasia. A further significant finding in this series was that the average age of those patients showing abnormal glucose tolerance curves was 11 years older than those showing normal tolerance curves, 63 as against 52. Women who develop obesity at the time of the menopause are frequently those with impaired glucose tolerance. It is particularly in this type of patient, who develops a diffuse type of endometrial carcinoma whilst still menstruating or shortly after a late menopause, that there may be a common ætiological factor originating in the anterior pituitary. On the other hand, in the much older age group in whom obesity is less common and who are, in fact, frequently thin, endometrial cancer tends to be more localized in the fundus of the uterus with atrophic endometrium elsewhere. A proportion of these patients may show impaired glucose tolerance merely because of their advanced age. The relative importance of obesity and age require

a much more detailed study in relation to endometrial cancer than has ever been done in any of the series of cases so far investigated and reported in the literature. If a patient is middle-aged and obese, or elderly and thin, impaired carbohydrate tolerance is very likely to be found, regardless of any gynæcological disorder from which she may be suffering.

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APPLICATIONS OF CHROMOSOME STUDIES IN OBSTETRICS AND GYNÆCOLOGY*

by

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Barr and Bertram (1949), working with cats, described "nuclear satellites" in nerve cells which only occurred in the cells of females. Within a few years it was shown that these "satellites", now usually termed Barr bodies or sex chromatin, could be demonstrated in the nuclei of cells from most tissues in many female mammals, and that in occasional individuals "nuclear sex" and apparent or phenotypic sex did not agree. From this and their staining properties it seemed obvious that these chromatin masses reflected the situation of the X-chromosome.

In succeeding years remarkable advances in technique of display of mammalian chromosomes, involving tissue culture, stopping of cell division in metaphase and flattening of cell nuclei on slides have permitted for the first time routine display of human chromosomes. Soon these techniques were being used to examine the chromosomes of abnormal individuals and in 1959 the first anomaly, the extra small chromosome in mongolism was discovered (Lejeune, Turpin and Gautier, 1959). Since then a remarkable array of anomalies of number and of structure of chromosomes has been demonstrated. A high proportion of these relate to alterations of sex chromosome number.

Disorders of sexual development had long been studied and it seemed reasonable to hope that chromosome anomalies would relate to specific clinical states or at least to closely related groups of conditions. Such high hopes have not, however, been fully realized. Cases appearing to form reasonably homogeneous groups on clinical grounds may show (a) normal chromosome constitutions (karyotypes), (b) a particular abnormal karyotype in a highly significant proportion

* A Glossary of genetical and cytological terms appears at the end of this chapter as Appendix I.

of cases, or (c) mosaicism, which includes that abnormal karyotype. (In this context mosaicism means the occurrence of clones or cell lines of two or more different karyotypes in the same individual.)

Sex Chromatin and the Sex Chromosomes

Sex Chromatin

Sex chromatin or Barr bodies can be demonstrated in female cell nuclei from sections of most tissues which have been suitably fixed and stained. Nuclear sex can also be determined in polymorph leucocytes in blood films but findings are less constant and less easy to interpret. The most convenient sources of cells for sexing are buccal smears, where the bodies can be demonstrated in over 30% of cells, and vaginal smears in over 60% of cells, provided good techniques are used. These bodies usually lie against the nuclear membrane and characteristically present two convex faces towards the centre of the nucleus (Fig. 40). A few similar bodies are sometimes
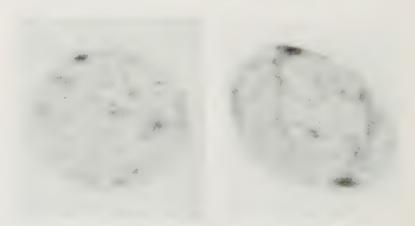
Fig. 40. Cells from buccal smears showing one and two Barr bodies.

seen in male cells but the proportion does not exceed 3% unless there is misidentification.

It is now known that the number of Barr bodies is one less than the number of X-chromosomes in the cell. An exception to this for which no explanation can be advanced has been found in a subject who had only one X-chromosome but had Barr bodies (Grumbach, Morishima and Chu, 1960). In another case (Miller *et al.*, 1963) two sex chromatin bodies of different sizes were found in buccal

smear cells of an individual whose leucocyte chromosomes were mosaic XO/Xx. However, these must be seen against the background of many thousands of instances where the rule holds, and the buccal mucosa cells which are those usually examined for sex chromatin may have only one cell line although the subjects were mosaic.

Sex Chromatin and the Number of X-chromosomes

The sex chromatin is believed to be a single condensed and pyknotic X-chromosome (Ohno and Makino, 1961). Morishima, Grumbach and Taylor (1962) by autoradiographic techniques demonstrated delay in DNA synthesis in interphase on one X-chromosome in females relative to the other X and to all the autosomes, indicating that the two X-chromosomes were not alike in another respect and it has now been shown that the late synthesizing X is almost certainly the one which is condensed and forms the Barr body. Lyon (1961 and 1962) advanced her hypothesis of dosage compensation on X-chromosomes starting from the behaviour of coat colour genes on the X-chromosome in the mouse where the male, having only one X-chromosome, is of the uniform mutation colour while the heterozygous female has banding or patchiness of the normal and the mutation coat colours with no overlap.

It is postulated that a large proportion of the genes on one X-chromosome in each female cell is inactivated, so achieving the same dosage to both sexes of most genes on the X-chromosome. The inactivation appears to be random in respect of parental origin so that, on average, half a female's cells have an active X of maternal and half of paternal origin. In the rabbit sex chromatin cannot be seen in ova or the cells of early cleavage divisions, but only appears after this stage. Park (1957) showed that sex chromatin was present in human embryos by 17 days and Thorburn (1964) has demonstrated these bodies in the cells of a human embryo thought to be only 13 days old.

Inactivation appears to apply to any additional X-chromosomes in the karyotype so that, for example, an XXX individual would have two X's inactivated and two sex chromatin bodies in her cells, so explaining the Barr body number being one less than the number of X-chromosomes.

The Normal Chromosome Complement in Man

Normal somatic cells have the diploid, 46 chromosome number with 22 pairs of autosomes and a pair of X and X, or X and Y chromosomes according to sex. In *mitosis or somatic cell division*

the chromosomes split along their length into chromatids and one of each of these pairs passes into the daughter cell, so preserving the diploid 46 number. The necessary deoxyribonucleic acid (DNA) is synthesized in interphase and the full complement for both daughter cells is available when the first signs of impending mitosis are seen in the nucleus.
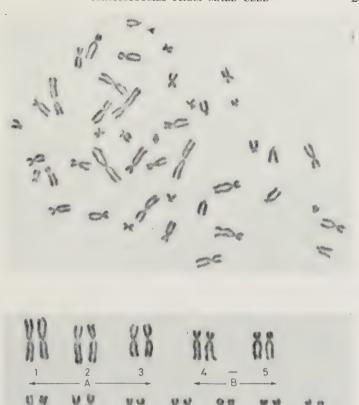
Chromosomes are most easily studied and identified in the metaphase stage of cell division. At this stage they are contracted and discrete from each other. They have already split at their extremities into the chromatids, which will pass to daughter cells but the future chromatids are still held together at their centromeres. In the living cell they are being arranged on the plane of the diameter of the cell nucleus (the metaphase plate), preparatory to the final separation of the chromatids. When the cell nucleus is ruptured (by treatment with hypotonic saline and gentle pressure) they fall on the slide or coverslip forming patterns as in Figs. 41 and 42, which show the metaphase chromosomes from cells of a male and of a female and their appearance when cut out from the photographs, paired and arranged according to a plan agreed by cytologists at conferences in Denver (1960) and London (1963).

The available ways of identifying individual chromosomes include overall length, relative lengths of the arms measured from the centromere, the occurrence of satellites and of constrictions which experience shows are likely to occur in certain positions in specific chromosomes. Further, there is some degree of variation in overall length of chromosomes, notably in pairs 2 and 16 and in the Y.

It will be seen that the X-chromosomes are very similar to those in the second row (Group C). There are still some cytologists who think that they can positively identify X-chromosomes, but the majority feel that this is impossible. However, one of the X-chromosomes in the female (or more than one in multiple X karyotypes) can be identified positively by autoradiographic techniques. The Y chromosome is also difficult at times to separate from those of pairs 21 and 22 but usually it can be identified with confidence.

The Chromosomes in Germ Cell Maturation

In order to maintain the diploid number of the species in the next generation it is essential that the male and female gametes which by syngamy form the zygote, should have the half (or "haploid") chromosomes number. This is achieved in meiosis. In the first meiotic division instead of, as in mitosis, dividing into chromatids, one whole chromosome of each pair (already showing the partial
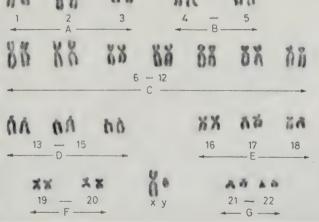
Fig. 41. Chromosomes from nucleus of a male cell in the metaphase stage of mitosis. (Above)
The chromosomes paired, numbered and lettered in accordance with the Denver and London conventions. (Below)
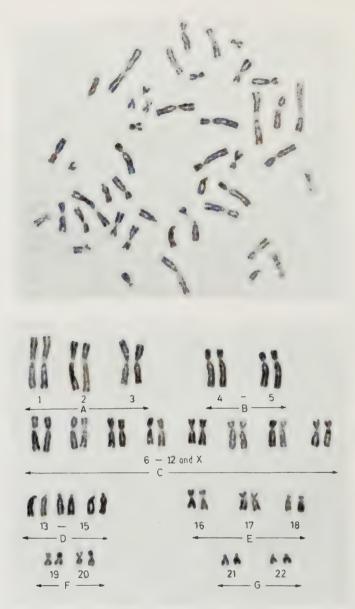
FIG. 42. Chromosomes from nucleus of a female cell in the metaphase
stage of mitosis. (Above)
   The chromosomes paired, numbered and lettered in accordance
with the Denver and London conventions. (Below)

splitting as in mitotic division) passes into each daughter cell which therefore has 23 chromosomes. In the second meiotic division the separation of the chromatids is completed and one chromatid passes into each daughter cell so maintaining the haploid number, 23, of chromosomes. All the DNA necessary for the mature gametes has already been synthesized in the last diploid cell in the line—the primary "cyte". However, germ cell maturation differs if not in principle, at least in timing in the sexes.

Spermatogenesis

It will be remembered that the primary differentiated germ cells are diploid, that is having the usual diploid number of chromosomes of the somatic cells, 46, and are termed gonia. Spermatogonia are present in the testicular tubules at birth and persist throughout life. They further divide by mitosis several times before reaching the last diploid cell stage before meiosis, the primary spermatocyte. The division of primary (diploid) to secondary (haploid) spermatocytes is characterized by the passage of one of each pair of chromosomes into each secondary spermatocyte so determining reduction of the chromosome number to the "haploid" number of 23. (The first meiotic division.) Thereafter the secondary spermatocyte divides to form two spermatids. (The second meiotic division.) These, without further division, differentiate into spermatozoa and are released into the lumen of the tubules.

Oogenesis

In contrast all the oogonia which a woman will ever have are believed to be present before birth and by about the first 14 days of life all have divided to form the primary (diploid) oocytes. These oocytes remain in the same stage of cell division (the so-called dictyate stage of pachytene), with homologous pairs of elongated chromosomes lying closely opposed to each other. After puberty, in each cycle, groups of them begin to mature. Of these only one ovum or occasionally two, proceed beyond the preliminary stages of follicle formation, enlarge and bulge on the surface of the ovary preparatory to ovulation.

The first of the two meiotic divisions occurs about the time when the follicle ruptures, one of the haploid nuclei forming the first polar body. The second division, involving separation of chromatids, probably occurs only when a sperm has entered the ovum.

Diagrammatically the stages of germ cell maturation in the sexes are shown in Fig. 43. The behaviour of the chromosomes (the sex
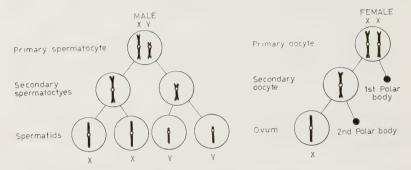
FIG. 43. Diagrammatic representation of meiosis in male and female germ cells.
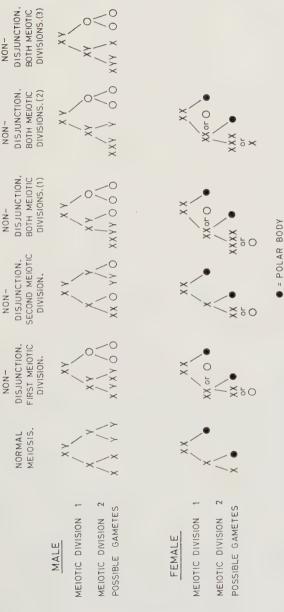
chromosomes only being shown for clarity) is shown in relation to these stages. For details of germ cell maturation (meiotic) and somatic (mitotic) divisions standard textbooks of embryology and cytology should be consulted.

Aneuploidy

It is convenient to consider aneuploidy or abnormal chromosome number in the zygote, mainly in respect of the sex chromosomes. Such aneuploidies outnumber all those affecting autosomes so far encountered. Contributing factors to this may be lesser stability of the XY pairs in meiotic divisions, the possibility of screening larger numbers of cases by nuclear sexing, and the fact that losses of or duplications of autosomes more commonly determine death of the embryo and so are not identified.

Unequal distributions of chromosomes to daughter cells may occur in mitotic divisions preceding the gonial stages, i.e. in primitive anlage germ cells. They may also occur in mitotic divisions of gonial cells which will, in the female, be in fœtal life and in the male at any time during life. Finally, they may occur during meiosis. There is some evidence that so-called non-disjunction occurring in one cell division predisposes to further unequal distribution in succeeding divisions of the daughter cells.

Fig. 44 sets out diagrammatically the type of gametes in respect of the sex chromosomes which could result in the two sexes from normal meiosis and from meiosis involving non-disjunction in the first, second or both meiotic divisions. It will be clear that a large

Fig. 44. The figure shows diagrammatically the different end results in terms of numbers of the sex chromosomes in gametes resulting from unequal distribution of these chromosomes in different germcell divisions ("Non-disjunction").

number of possible aneuploid zygotes could arise from combinations of euploid spermatozoa or ova and aneuploid gametes from the other partner.

Studies, using as markers colour vision and the Xg blood groups, both determined by genes on the X-chromosome, have indicated in some cases in which parent and in which meiotic division the non-disjunction probably occurred.

There is considerable evidence from the mouse that X or Y chromosomes from either male or female pro-nuclei may be lost in the process of syngamy when the sperm and ovum pro-nuclei in the cytoplasm of the ovum fuse to form the diploid nucleus of the zygote. It is possible that some XO individuals arise in this way from loss of an X or a Y chromosome. It may further be noted that the frequency of sex chromosome loss from a pro-nucleus may be significantly increased by relatively small doses (e.g. 25 rads) of rapidly delivered radiation to the very late germ cell stages or to the fertilized ovum before syngamy.

Mosaicism

Non-disjunction may also occur in the mitotic cleavage divisions of the zygote and is the origin of mosaicism. Again there is probably an increased likelihood for this to occur if the zygote was aneuploid. Some of the aneuploid cells arising in the mitotic cleavage divisions may survive, e.g. if instead of two XY daughter cells one is XXY and the other YO, the YO cell line may not survive, leaving a non-mosaic but XXY individual.

The following mosaic karyotypes including X and Y chromosomes represent all or most of those so far found. From reference to Fig. 44 it will be seen that some must have originated, or had a contribution from non-disjunction arising in cleavage divisions.

XX/XO	XO/XY	XX/XY	XX/XXX
XO/XXX	XX/XXXX	XO/XXY	XO/XXXY
XO/XYY	XY/XXY	XY/XXXY	XY/XYY
XY/XXYY	XX/XXXY	XX/XXY/XXYYY	XX/XXY/XXXY
XY/XXY/XXYY	XO/XX/XXX	XY/Xy/XXXy	XO/XY/XXY
		XX/XXY/XY	

Association of Sex Chromosome and Autosomal Aneuploidies

There appears to be a tendency for aneuploidy of more than one chromosome pair to occur in the same subject. Thus, individuals with XXY and trisomy 21 (mongolism) karyotypes have been

described at least five times (e.g. Ford *et al.*, 1959a; Hustinx *et al.*, 1961), as has mongolism (trisomy 21) and XX/XO mosaicism (Van Wijck, Blankenborg and Stolte, 1964), and mongolism (trisomy 21) and X°XX (Day *et al.*, 1963). XXX and trisomy 18 has also been described (Uchida and Bowman, 1961).

A similar tendency for different aneuploidies to occur in more than one member of a sibship is suggested by the occurrence of Klinefelter's syndrome (XXY) and mongolism (trisomy 21) in the same sibship (Wright *et al.*, 1963), Johnston and Petrakis (1963) described XO and trisomy 21 mongol individuals in the same sibship; and by other examples.

Leukæmia and Aneuploidy

Space does not permit consideration of chromosomal anomalies in patients with leukæmia or their sibs. It may be noted, however, that leukæmia frequency is raised in mongols and their sibs and that acute leukæmia has been described in two sibs of an XY/XXY mosaic (Baikie *et al.*, 1961) and in an XO/XXX mosaic (Lewis, Poulding and Eastham, 1963). Finally, Miller and co-workers (1961) have described a sibship which included an XXXXY male, a leukæmic male and two trisomy 21 mongol females.

Structural Changes in X-Chromosomes

Isochromosome-X

Isochromosomes are chromosomes consisting of two identical arms. In the case of the X-chromosome which is submetacentric, having the centromere rather nearer one end than the other, iso-chromosomes consisting of two short and/or two long arms can occur (Fraccaro *et al.*, 1960).

The phenomenon could arise in various ways, but the most likely explanation is that one arm of the chromosome breaks close to the centromere and is lost (Fig. 45b). The other which has the centromere splits into chromatids and both pass with the centromere to a daughter cell. In the next cell division both chromatid arms divide and become aligned on either side of the centromere so resulting in a chromosome with equal arms (Fig. 45d and e).

It is rather difficult to be certain of the interpretation of micro-scopic findings in these cases but some are almost certainly genuine as is shown by the clinical associations, linkage relationships, DNA measurements and autoradiographic techniques. Most, if not all
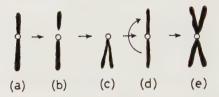
Fig. 45. Diagrammatic representation of formation of an isochromosome.
  (a) The normal chromosome.
  (b) A break has occurred in the short arm near the centromere, the acentric fragment is lost.
  (c) Showing the formation of two chromatids of long arms.
  (d) Reorientation of the two long arms relative to the centromere.
  (e) Formation of chromatids at the next cell division.

of these isochromosomes appear to be of the longer arm of the X-chromosome and some occur as part of a mosaicism.

From clinical studies which are discussed below it would appear that it is absence of the shorter arm of the X-chromosome which is associated with the gonadal dysgenesis in Turner's syndrome (Lindsten *et al.*, 1963*a*). There is also suggestive evidence that the gene locus at which the Xg blood group antigens is determined is also on the short arm of the X-chromosome (Lindsten *et al.*, 1963*b*).

Ring Chromosome of X

Ring chromosomes arise when two breaks occur and two terminal portions are lost. The broken ends of the remainder of the chromosome then join. If the centromere is included in the ring the chromosomes may divide regularly and pass into daughter cells. The association of ring X-chromosomes with ovarian dysgenesis is discussed later.

Other Structural Changes in the X-Chromosome

An individual with two cell lines, one XO and the other with one normal X and an X with short arms deleted (denoted by Xx) was found in a deaf girl of short stature and ovarian dysgenesis (Lindsten, 1963).

In another case (Conen and Erkman, 1963), an XX/Xx karyotype is described in a baby with ambiguous genitalia. Structural changes in X-chromosomes have also been described by Jacobs and co-workers (1961) and Polani (1961).

Frequencies of Anomalies of the Sex Chromosomes

Frequencies in the Newborn

Moore (1959) showed that in 3,715 newborn babies nuclear and chromosomal sex were concordant in all 1,804 females; but 5 of 1,911 males showed sex chromatin bodies in buccal smears. Bergemann (1961) had a similar experience and others have found phenotypic males of female nuclear sex in small series.

Maclean and co-workers (1964) found 21 chromatin positive newborn babies in 10,725 males (1·96 per 1,000). Of 10,000 female babies 4 were chromatin negative (0·4 per 1,000) and 12 had two sex chromatin bodies (1·2 per 1,000). Of 18 males in whom chromosome studies were carried out, 12 were XXY and 1 was XXYY, while 5 were XY/XXY mosaics. In 13 females whose chromosomes were examined, 9 were XXX, 3 were XO and 1 was XO/Xx. There have also been several other smaller studies where findings were not substantially different.

Some care has to be taken in nuclear sexing from a buccal smear in newborn babies. Taylor (1963) showed that in the first 2 days of life a number of smears from females showed very few Barr bodies but that subsequently the numbers increased.

Changes with Age

Jacobs, Court Brown and Doll (1961) and Jacobs and co-workers (1963) found an increase in the number of aneuploid cells in blood cultures which was related to age. With advancing age the proportion of 45 chromosome cells increases and the loss appears to be predominantly of an X-chromosome in females and a Y in males.

Frequencies in the Mentally Retarded

It has been found that an excess number of sex chromosomes is usually associated with a moderate fall in intelligence. Prader and co-workers (1958) found 8 chromatin positive boys in a sample of 336 who had an I.Q. range of about 75–85 and since then a relatively high incidence of sex chromosomal anomalies has been found in several samples of retarded children. Maclean and co-workers (1962) took buccal smears of 2,607 males and 1,907 females in institutions for mental defectives where the age and the I.Q. range was considerable and included many low grade defectives. In this series the chromosomes were examined in all 37 patients discordant in phenotypic and nuclear sex. There were 28 phenotypic males and 9 females. The males were mostly XXY or XXXY but 11 were

mosaic for various abnormal combinations. Seven of the females were XXX. One was mosaic (XX/XXX) and one was XO. The paper summarizes and reviews previous contributions on sex chromosome complements of the mentally retarded. De la Chapelle (1963) reports from Finland a rather higher frequency, 5·6 per 1,000, of sex chromosomal aberrations in mentally defective girls. Of 7 cases, 3 were XO, 2 XXX and there were 2 mosaics, 1 XO/Xx, and 1 XO/XX(i) (long arms).

Most authors doubt whether there is any drop in mean intelligence in XO subjects but a careful study of Lindsten (1963) appears to indicate that there is a reduction, although it is smaller than in subjects with multiple X karyotypes.

The Contribution of Chromosomal Abnormalities to Abortion

Abnormal Karyotypes of Aborted Embryos and Fœtuses

As mentioned previously, it is likely that there is some contribution of gross chromosomal damage to zygotes which fail to implant or die immediately after implantation and are absorbed. The aberrations found in later recognizable abortions appear to be mainly of the same types as found in the live born. All the sex chromosome aberrations already mentioned have been found in addition to trisomies 21 (mongolism), trisomies of the 13/15, and of the 17/18 groups, and two possible cases of a missing chromosome of the 13/15 group. In addition, isolated examples of complete or partially triploid (69 chromosomes) fœtuses have been identified (Carr, 1964; Penrose and Delhanty, 1961). It is difficult to get a proper sample of aberrations as there are considerable technical difficulties in growing amnion or chorion and only a small proportion of the earlier embryos and fœtuses are recovered or are sufficiently free from maceration or infection to give good cultures.

Carr (1964) reports some rather startling data from Canada. Of 122 spontaneous abortions before the 28th week of pregnancy 28 (23%) had major chromosomal abnormalities. These anomalies were B trisomy 1, C trisomy 2, D trisomy 4, E trisomy 5, G trisomy 3, XO 6, triploid (69 chromosomes) 6 (5 were XXY, 1 was XYY) and tetraploid (102 chromosomes) 1. These are indeed remarkable figures. There is no reason to suppose selection of abortions for study and no comparable series with stated number of normal and abnormal karyotypes have been reported but it is clear that of many abortions examined in many laboratories only few have been

reported. We shall have to wait until further series are published to assess the contribution of chromosomal abnormalities to abortions and to try to relate them to time of loss and other clinical findings.

Recurrent Abortion

Only one instance has been reported of abnormal chromosomes in the parents of several abortions. Schmid (1962) found an extra abnormal short acrocentric chromosome in the husband of a woman whose first two pregnancies ended in abortion. Experience in the laboratory of the writer's unit has shown karyotypes of many pairs of parents of recurrent abortions to be normal.

It has been suspected that in some instances where a woman has had several abortions, or abortions and deformed children, she or her husband is what is called a "balanced translocate", that is to say, she has all the normal chromosomal material but there have been exchanges of parts between chromosomes or (less accurately to fit the term "balanced translocate") two chromosomes are attached. These two situations are shown diagrammatically in Figs. 46 and 47. It will be seen that there is a fourfold segregation of possible zygotes and it is possible that either, or both, unbalanced zygotes (i.e. with missing part of one chromosome and an extra part of the other or an entire missing or extra (attached) chromosome) may determine abortion. Instances of inheritance of such situations where one unbalanced zygote results in a malformed child are discussed later.

It may confidently be predicted that instances where the abortion can be proved to be an unbalanced translocate will be found although probably most of these zygotes are eliminated before or shortly after implantation.

Chromosomal Anomalies and Congenital Malformations

Of all developmental anomalies which present at birth and can be recognized by the naked eye only a small proportion are determined by single gene mutations. The majority appear to be determined by ill-understood mechanisms involving varying contributions from the genotype and interaction with the intra-uterine environment. For example, in embryos damaged by rubella, by radiation *in utero*, or by drugs such as thalidomide, the contribution is almost entirely environmental and there are other malformations such as most anencephalies where indirect evidence suggests that the genotypic contribution is small.

FIG. 46
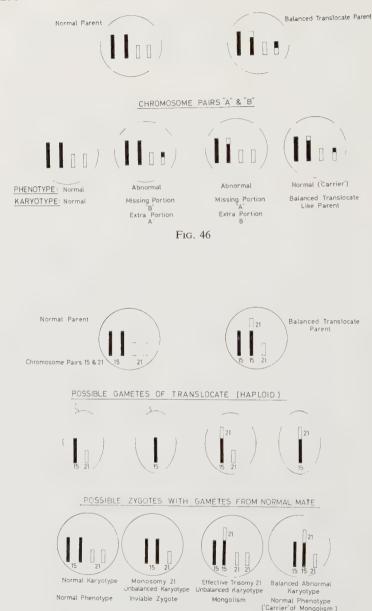
FIG. 47

Of those determined by abnormal chromosomes in the zygote, mongolism is the best known and by far the most frequent, occurring in perhaps 0.2% of births in this country. It may well be that chromosomal damage too small to be detected by present methods causes other malformations, but at present mongolism and syndromes (which are seldom recognized at birth) determined by anomalies of sex chromosomes contribute the great majority of recognizable chromosomal abnormalities. From time to time small chromosomal anomalies have been detected in malformed stillbirths or infants, but specific changes are not found consistently. Only experience will determine the significance of such isolated findings. So far chromosomal examinations have been predominantly on abnormal subjects so that we have relatively little knowledge about the range of small harmless chromosomal variations, particularly in respect of the autosomes.

Mongolism

All mongols where the clinical diagnosis is unequivocal have been found on investigation to have an extra No. 21 chromosome or at least the major part of such a chromosome. The extra chromosome may be discrete, determining "regular" 47 chromosome mongolism. It may be translocated or attached to another chromosome so determining 46 chromosome mongolism. Finally, it may represent the attached duplicated arms of an isochromosome.

47 Chromosome Mongolism

The great majority, perhaps 96%, of mongols have 47 chromosomes. The aneuploidy appears usually to arise in meiosis in the mother and the frequency of such accidents increases with maternal age. The condition may, however, arise in the cleavage divisions of the zygote and give rise to mosaicism. No individual with 45 normal chromosomes but missing a No. 21 has been found and the condition is presumed to be lethal. Further no cell lines with a missing No. 21 chromosome have been found so that it is probable that most such cells die if they arise by non-disjunction in a cleavage division.

Mosaic individuals usually have 46 and 47 chromosome cell lines but three cell lines have been described. Non-disjunction at the first division of the zygote would result in an individual who was a "regular" mongol with all cells having 47 chromosomes, being trisomic for No. 21 as the 45 cell line monosomic for No. 21 would not survive. It is possible that some mongolism is so determined.

Clarke, Edwards and Smallpeice (1961) described a girl with minimal stigmata of mongolism who had an intelligence quotient of 100. She had about 50% of cells trisomic for No. 21 in skin fibroblasts but none in white blood cells. Subsequently several authors (e.g. Blank *et al.*, 1962; Smith *et al.*, 1962) have described such mosaicism in phenotypically normal mothers of 47 chromosome mongol children.

More than one 47 chromosome mongol is occasionally born to the same mother. This may be due to "chance" or it may be because the mother is mosaic 46/47, and a 24 chromosome ovum (having two Nos. 21) has been fertilized. There is also much to suggest that certain parents, probably predominantly mothers, are especially liable to non-disjunction and have successive offspring who are aneuploid for the same or different chromosomes. Some examples have been quoted earlier. Genes determining such liability are known to occur in some animals.

46 Chromosome Mongolism

The extra whole or large part of a No. 21 chromosome determining mongolism is not discrete in these cases. The explanation could be:

1. The No. 21 chromosome may be attached to another chromosome (usually one of the "D" (13 to 15) group) or to a No. 22.
2. Two No. 21 chromosomes may have become attached to each other and so form a compound chromosome.
3. An isochromosome of the long arms of a No. 21 chromosome may have arisen.

In each case where a gamete has such a chromosome the addition of a single No. 21 chromosome from the other partner will determine a zygote which is "effectively" trisomic for No. 21.

These changes may arise in meiosis, although isochromosome No. 21 could not arise in a first meiotic division. They can also arise in mitotic cleavage divisions so that subjects may be mosaic for 45 and 46 chromosome cell lines. It follows that they may be transmitted by mosaic individuals who have no stigmata or only minor stigmata of mongolism.

Transmitted Translocations

In the case of (1) and (2) above (the translocations), however, the transmission may be differently determined. A parent may have only 45 chromosomes but still have two effective No. 21 chromosomes and so be of normal phenotype. This is because

there is one discrete No. 21 and another attached to another chromosome. This situation, as for attachment to a No. 15 chromosome is shown in Fig. 47. Such an individual is called a balanced translocate and it will be seen that the possible zygotes of such a parent who is married to a normal individual are of four possible types which would be expected to result in equal proportions in:

(a) individuals who have normal karyotypes;
(b) individuals who are normal phenotypically but have 45 chromosomes and balanced translocate karyotypes;
(c) zygotes monosomic for No. 21 which do not survive;
(d) 46 chromosome translocate mongols.

Forty-six chromosome mongolism determined by a 21-D translocation transmitted by a balanced translocate parent was first described by Penrose, Ellis and Delhanty (1960) and has since been reported on many occasions. Fig. 48 shows the pedigree of such a family. Polani and co-workers (1960) described a 46 chromosome 21-D translocate born to parents of normal karyotype, presumably having arisen in meiosis.

Chromosomes 21 and 22 cannot be distinguished microscopically. Thus, a 21-21 cannot be distinguished from a 21-22 compound chromosome. In turn neither can be distinguished from a 21 iso-

45 CHROMOSOME,
15/G, TRANSLOCATE "CARRIER".
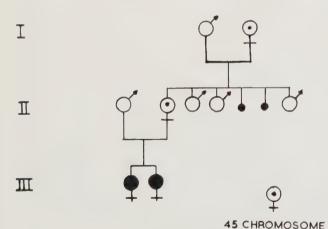
FIG. 48. Diagrammatic pedigree of a family where two mongol girls III 1 and III 2 occurred. II 1 and I 2 were proved cytologically to be 47 chromosome 15/21 translocate "carriers".

chromosome. However, an isochromosome can only be transmitted from parent to child if the parent is mosaic for an isochromosome (unless in the rare situation where a mongol individual is a parent).

The situation where an individual is a balanced 21-21 translocate is remarkable in that such a 45 chromosome parent can only produce gametes having, in respect of the 21 chromosomes, either none or a compound chromosome composed of two 21's. It follows that all zygotes resulting from syngamy of such gametes and those of a normal parent will either fail to develop or develop into mongol fœtuses.

The impossibility of distinguishing microscopically between (i) the "G" group chromosomes 21 and 22, (ii) an isochromosome of either, and (iii) a 21-21, 21-22 or 22-22 compound chromosome makes for difficulty in estimating the genetic prognosis in these cases. Only a mosaic individual (unless a mongol) could transmit an isochromosome and if any normal child has been born to a parent with two of these small acrocentrics attached then the parent cannot be a 21-21 translocate. These translocations involving Nos. 21 and 22 were described by Penrose, Ellis and Delhanty (1960) and Hamerton (1962) and further examples have been described by Shaw (1962), Benirschke and co-workers (1962) and Bavin, Marshall and Delhanty (1963).

Penrose (1962) suggests that where G-G translocates are born to parents of normal karyotype the paternal age is raised. In the cases reviewed the mean paternal age was 42·5 years, which was $18 \pm 2·3$ years above a control mean.

The most common mongol karyotypes are set out in Fig. 49, which shows chromosomes of the "D" and "G" groups in the different types of mongols. There are a number of further complications which cannot be dealt with in this condensed review.

Need for Cytological Investigations in Mongolism

It will be seen, however, that when a mother of any age has a mongol child the chromosomal situation should be investigated as thoroughly as possible, if certain recurring and important questions are to be answered. The usual one is "What is the chance of having another mongol child from a future pregnancy?" It will be clear from the foregoing that there is another question which is unlikely to be raised by the patients, namely, "Are any of my normal children likely to be balanced translocate carriers?"

The work involved is enormous and cannot be undertaken with the present laboratory provision in this country, but it seems to

MONGOLISM

CONDITION AND KARYOTYPE OF CHILD	DIAGRAMMATIC REPRESENTATION OF 'D' AND 'G' GROUP CHROMOSOMES					POSSIBLE CHROMOSOMAL ANOMALIES IN PARENTS.
	13	14	15	21	22	
NORMAL	ΛΛ	ΛΛ	ΛΛ	ΧΧ	ΛΛ	
REGULAR MONGOL. 47 CHROMOSOMES. TRISOMY 21	ΛΛ	ΛΛ	ΛΛ	ΧΧΧ	ΛΛ	A PARENT MAY BE 46:47 CHROMOSOME MOSAIC.
MONGOL. 21:15 TRANSLOCATE, 46 CHROMOSOMES	ΛΛ	ΛΛ	ΛΛ^{21}	ΛΛ	ΧΧ	A PARENT MAY BE A 45 CHROMOSOME 'BALANCED TRANSLOCATE'
MONGOL. 21:22 TRANSLOCATE, 46 CHROMOSOMES	ΛΛ	ΛΛ	ΛΛ	ΛΛ	$\overset{21}{ΛΧ}$	OR BE MOSAIC FOR SUCH A CELL LINE.
MONGOL. 21:21 TRANSLOCATE, 46 CHROMOSOMES	ΛΛ	ΛΛ	ΛΛ	$\overset{21}{ΛΧ}$	ΛΛ	
MONGOL. ISO-CHROMOSOME 21. 46 CHROMOSOMES	ΛΛ	ΛΛ	ΛΧ	$\overset{\uparrow}{ΛΧ}$ $\underset{\text{ISOCHROMOSOME}}{21}$	ΧΧ	A PARENT MAY BE MOSAIC FOR A 45 CHROMOSOME (INCLUDING ISOCHROMOSOME 21) CELL LINE.

Fig. 49.

the writer that when a mongol child is born, irrespective of the age of the mother the chromosomes of the child and of both parents should be examined, and the situation clarified as far as possible. It seems particularly important to search for mosaicism in parents as this is the parental defect most difficult to detect and most easily missed. This mosaicism may only be detected after examination of cells from many parental tissues.

If any of the known mechanisms of transmission of mongolism are detected then estimation of risks to a future child can be given with reasonable confidence, although the relevant proportion of the two or more cell lines in a mosaic parent may differ in different tissues so that the ratio in the gonads cannot be determined and may be very different from that detected in any somatic tissue. Cytological investigation will also make it clear whether phenotypically normal sibs should be investigated.

However, the great majority of mongols are the only affected children in a sibship and the parents have normal karyotypes. In such a case the risk of recurrence has to be estimated empirically. Meiotic non-disjunction appears to increase exponentially with maternal age. No sufficiently large series of cases has as yet been fully investigated to enable this maternal age effect to be given with full confidence in respect of mothers of single unexplained mongol children, but the frequency of birth of mongols to mothers of varying maternal age is approximately: under 30 years: 1/1,000; 30–34: 1·5/1,000; 35–39: 3/1,000; 40–45: 10/1,000; rising very steeply thereafter.

In order to allow for missed mosaicism and the tendency to non-disjunction in certain parents, after a first 47 chromosome mongol child has been born to a woman of given age and the parents are of normal karyotypes the risk to a subsequent child should probably be given as three times the above frequencies.

Trisomies of Other Autosomes

Trisomy of 16.17.18 (E) Group

Edwards and co-workers (1960) reported trisomy of one of the E group chromosomes in a child with multiple malformations and numerous other cases have since been described. It is believed that the extra chromosome is usually one of the group (either No. 17 or No. 18) and there is a rather characteristic syndrome associated, so that some observers feel that a clinical diagnosis will almost invariably be found to be associated with the specific trisomy. The

writer is not entirely convinced, having seen several cases showing a characteristic association of the signs mentioned below but having a normal karyotype. Characteristically the infants are small at birth. They have a small head with rather peaked low-set ears with the lower ends tilted forward. There is a degree of micrognathia. The sternum is short and broad often with a depression over the lower end and the pelvis is narrow. The fingers are characteristically flexed with the thumbs in the palms and clinodactyly of the second and fourth fingers which are usually under the third. A very high proportion have congenital malformations of the heart, but no specific type appears to be associated. Various anomalies of urinary tract and gut have also been reported. The sex ratio of cases so far recorded suggests a slight excess of males. Another characteristic finding is absence of whorls or loops on the finger tips. They are usually replaced by irregularly parallel horizontal ridges.

Trisomy of the 13-15 (D) Group

This was first described by Patau and co-workers (1960) but since then many cases have been described. Again the relative constancy of the clinical picture suggests that it is predominantly one chromosome of the group which is trisomic. The infants are also small at birth and a high proportion have harelip and cleft palate, often severe. In the absence of such clefts the face is usually dysplasic. Microphthalmia and anophthalmia are usual and a few children who survived long enough for testing have been deaf. Double uterus or hypospadias have occurred in many cases. Digital anomalies, usually ulnar polydactyly are common. The ear pinnæ are often flattened. Hæmangiomata and telangiectasis are common. There is usually a single transverse palmar crease and the ridge patterns in hands and fingers are abnormal. The infants, when placed on their backs, usually lie with their upper arms everted lying in the cot, their elbows flexed at right angles and their clenched hands facing palms upwards.

Two unrelated boys with D group trisomy reported by Becak, Becak and Smith (1963) had generalized analgesia but none of the signs described in Patau's cases. Subsequently Becak, Becak and Andrade (1964) reported on 5 other children with generalized analgesia who were examined. Four had one or two extra chromosomes of the 13-15 group. In one case the extra acrocentric of the 13-15 group was attached to a small acrocentric of the 21-22 group. In two cases normal fathers had an extra chromosome of the D group. A number of other cases of congenital analgesia have,

however, proved to have normal karyotypes. The pattern of segregation of these cases and the finding of parental consanguinity suggests determination by a recessive gene mutation. Presumably these cases represent trisomy of a different chromosome of the D group from those described by Patau.

Huehns, Lutzner and Hecht (1964) found specific abnormalities, best seen by phase contrast microscopy, of the nuclei of blood neutrophils of patients with D (13-15) trisomy. There were between one and six small sessile Feulgen-positive projections from the nuclear lobes. These main lobes were distorted and the chromatin pattern coarse. These findings have been confirmed by others only in cells from patients with D trisomy, and they appear to represent specific nuclear disorganization which in the absence of facilities for chromosomal analyses may be taken as diagnostic.

Other Trisomies

Probable or possible trisomies of other chromosomes have been described. They are too numerous to discuss here and in some cases the interpretation of findings is rather uncertain. One completely triploid (69 chromosomes) individual has been described by Böök and Santesson (1960) and a mentally defective boy with hemi-hypertrophy who appears to be mainly triploid on the hypertrophied side has been found by Ferrier and co-workers (1964). Subsequent findings in this and other laboratories in the usual type of hemi-hypertrophy without mental defect have not shown such anomalies.

Translocations

These have been described much less frequently than aneuploidies. Most involve the small acrocentric chromosomes (21 and 22) in mongolism or the larger acrocentric group D. However, 1-G (Edwards *et al.*, 1963) and 2-C (Clarke *et al.*, 1964) translocations with balanced translocate parents and unbalanced offspring have been reported. In the latter case also a balanced translocate offspring was discovered.

Caution is needed, however, in attributing anomalies to unbalanced translocates, particularly where the missing or duplicated parts of chromosomes are small or the cytological situation in other members of the family do not point strongly to this interpretation. Jacobs and co-workers (1964) report a family where there were translocations between D and E group chromosomes. Individuals in the family with "normal", "balanced" and "unbalanced" translocations all appeared normal clinically.

Other Structural Chromosomal Changes

Deletions of parts of arms of the E group chromosomes have been described in dwarfed and mentally defective children. Ring chromosomes replacing one in the D group have been reported on three occasions but the syndromes in the infants vary, probably indicating that different numbers of the group are involved. In one fœtus, a stillborn female, there were defects of digits of hands and feet, talipes, microphthalmos, fusion of anterior cerebral hemispheres, arrhinencephaly, I.V. septal defect and bicornuate uterus (Bain and Gauld, 1963). Another (Wang *et al.*, 1962) had odd facies, micrognathia and large ears.

Lejeune and co-workers (1963) reported deletion of a short arm of a No. 5 chromosome in 3 children who had microphthalmia, wide distance between the eyes and rather flat face, severe mental retardation and a very characteristic whining cry like a cat. Subsequently many other cases have been found, most as yet unpublished. Preliminary evidence suggests an increase in maternal age.

Malformations which have not been Found to be Associated with Chromosomal Anomalies

A large number of specific traits and syndromes have been investigated for abnormal chromosome associations in recent years. The literature on negative findings alone is formidable and no doubt most laboratories have never bothered to publish such results. It would be impossible to list them all but perhaps it should be noted that no convincing association has been found with the group of malformations which are most common and severe, namely, those associated with gross abnormalities of development of the neural tube.

Finally, the future may well show that anomalies will be found in subjects with some example of malformations where previous findings were negative. This may result from better techniques or because the trait is of heterogeneous ætiology and only a minority of examples are determined by chromosomal anomalies.

The Sex Chromosomes in Patients likely to be Referred to Gynæcologists

Most patients referred to gynæcologists with conditions which may be associated with sex chromosome anomalies have primary amenorrhœa or some masculinization or ambiguity of the external genitalia. Of those with primary amenorrhœa about 40 % will prove

to have a chromosome aberration or to be of male (XY) karyotypes (Jacobs *et al.*, 1961). No reasonable estimate can at present be made of the proportion of those referred for ambiguity of the genitalia who have abnormal karyotypes but it is unlikely to be more than 10%.

Patients presenting for either of the above reasons or with a combination of amenorrhœa and malformation may prove to be of either gonadal sex or in rare instances to have no discoverable gonads. The chromosomal sex may be XX or XY or the karyotype may be abnormal by reason of aneuploidy or structural change in chromosomes in all cells. Alternatively, the patient may be mosaic for some of a great variety of cell lines.

There are so many varieties and combinations of phenotype, condition of gonads, and karyotypes, that it is impossible to devise tidy and logical groupings. The review which follows considers mainly a series of syndromes which have in common ovarian failure or abnormality and those conditions characterized by abnormal genitalia.

It seemed necessary to refer to conditions such as Ullrich's syndrome and the adrenal syndromes which, although not associated with abnormal karyotypes, are determined by single gene mutations which occasionally present problems of differential diagnosis.

Syndromes Associated with Ovarian Dysgenesis

It has become usual, when ovarian dysgenesis is associated with some or all of a specified spectrum of physical abnormalities to term the condition "Turner's syndrome" while cases not showing such morphological changes are termed "pure ovarian dysgenesis". However, in some instances the separation cannot be made with confidence either on a clinical or chromosomal basis. The terminology used to describe these cases has become extremely confused.

Turner's Syndrome

The original symptom complex described by Turner (1938) has been added to both before and since the discovery that most cases have an XO karyotype or are mosaic for XO cell lines. The typical signs are short squat physique, short neck frequently with webbing, rather "old" face for years, cubitus valgus, œdema of legs and feet and a variety of skeletal abnormalities. Coarctation of the aorta may be present in as many as 10% of cases. In Lindsten's (1963)

series 26 of 48 patients had abnormalities of kidneys and ureters. Evidence about intellectual retardation is still equivocal but there is probably a small mean reduction.

At puberty there is failure of development of the secondary sex characters. Breast development is slight and the nipples are wide spaced and hypoplastic. Body hair is scanty but with a feminine pattern. External genitalia are infantile in type with non-pigmentation of the labia majora, while the labia minora are small or vestigial. Exceptionally the clitoris is enlarged (Vaharu *et al.*, 1961, and other reports). The vagina and uterus are small and ovaries cannot be palpated.

At laparotomy ovaries are usually found to be vestigial or replaced by plaques or streaks of opaque glistening fibrous tissue in the broad ligament extending outwards towards the atria of the thin and often elongated Fallopian tubes. The tissue is like ovarian stroma but there is usually no sharp edge of demarcation from the fibrous tissue of the broad ligament. Occasionally, however, some mesenchymal ovarian tissue and atretic follicles can be distinguished microscopically. Most patients have primary amenorrhœa but a few have scanty irregular menstruation and one woman, demonstrated to be of XO karyotype, described by Bahner and co-workers (1960) menstruated regularly and gave birth to a normal (XY) boy. A recent review of 57 cases by Lindsten (1963) should be consulted for full descriptions of clinical and pathological findings. (It may be noted that in mice, XO individuals are apparently normal females and are fertile.)

Varney, Kenyon and Koch (1942) found that in these patients normal, or frequently excess amounts of F.S.H. were present in the urine. Such findings, with normal or lowered 17-ketosteroid excretion strongly point to primary non-functioning ovaries. Other evidence of normal levels and reserves of pituitary hormones in ovarian dysgenesis with XO karyotype is advanced by Fraccaro and co-workers (1960) and Louros and co-workers (1963).

A majority of these girls prove to have no sex chromatin in cells and to be of XO chromosome constitution, as first demonstrated by Ford and co-workers (1959b), but clinically indistinguishable cases may be XX (Aubert, 1962; de la Chapelle, 1962; etc.) or have one of a wide variety of mosaic karyotypes which include an XO cell line. XO/XX was described by Ford (1961) and subsequently by many others. Some, but not all of those having XX cell lines have Barr bodies in buccal smears. XO/XY karyotypes are reported by Jacobs and co-workers (1961) and others. (It may be noted as

discussed later that this XO/XY karyotype is associated with a remarkable number of other syndromes including true hermaphrodites, phenotypic males and females with some ambiguity of genitalia.) Other mosaic karyotypes described are XO/XXX (Jacobs *et al.*, 1961), XO/XX/XXX (Hayward and Cameron, 1961; and Grumbach and Morishima, 1961); and XO/XYY (Jacobs *et al.*, 1961). Jacobs and co-workers (1960) described an example of Xx karyotype in a patient with this syndrome and others have subsequently reported other cases and mosaics of XO/Xx karyotype.

In other cases there is an anomaly of an X chromosome which presumably interferes with its function. Thus XX(i) karyotypes have been described where one normal X chromosome was replaced by an isochromosome for the long arms of the X chromosome, the first being by Fraccaro and co-workers (1960). All isochromosomes of X so far described have been of the long arms which suggest that the gene material necessary for ovarian development is on the short arms. Lindsten and Tillinger (1962) and Luers, Struck and Nevinny-Stickel (1963) have described cases where the karyotype was XX(r), one X-chromosome being replaced by a small ring chromosome presumed to be derived from an X.

Finally, in a few females clinically of the type described, the sex chromosomes have proved to be XY and at laparotomy rudimentary testes or ovotestes have been found in the broad ligament.

Ovarian Dysgenesis without Signs of Turner's Syndrome

Other types of gonadal dysgenesis are found in patients who have primary ovarian dysgenesis but no stigmata of Turner's syndrome. A small proportion are of normal height, have XO karyotypes and streak gonads as in Turner's syndrome. Others have XX karyotypes and streak gonads.

The typical patient presents with primary amenorrhœa and is then found to have undergone little pubertal change. The genitalia are infantile and ovaries cannot be palpated. Pituitary gonadotrophins and corticotrophin levels are normal or increased and 17-ketosteroid excretion is normal.

Such a picture may be determined by any condition determining non-functioning ovaries and it is not surprising that a variety of gonadal situations are found at laparotomy. As already mentioned, some have streak gonads, others have small ovaries with the hypoplasia mainly affecting the cortex (Hoffenberg and Jackson, 1957), the medulla (Gordan *et al.*, 1955) or both cortex and medulla (Grumbach and Barr, 1958).

In other cases the ovaries may be small and fibrocystic. A majority of women with streak gonads or hypoplastic gonads are of normal female XX karyotype and it is probable that most of these cases are determined by single autosomal recessive genes, as multiple cases in sibships have often been described and in two reported instances the parents were related (Elliot, Sandler and Rabinowitz, 1959; and Stewart, 1960).

A minority of these women are, however, of XO karyotype or are mosaic XXX/XO as described by Jacobs and co-workers (1960), XO/XYY by Cooper and co-workers (1962). Two girls with primary amenorrhœa just over 5 ft. tall and not showing stigmata of Turner's syndrome had Xx karyotypes (Jacobs *et al.*, 1960; and de Grouchy *et al.*, 1961).

Most cases with small fibrocystic ovaries are also of XX karyotype and the condition has occurred in sisters so that this condition also may be determined by recessive gene mutations. However, Vague and co-workers (1956) and Wais (1960) have described the condition in women with no sex chromatin bodies in buccal smear cells.

Ovarian Dysgenesis with XY karyotype

There is another small group of cases which are difficult to place elsewhere and are classed by some as varieties of gonadal dysgenesis. (The term "pure gonadal dysgenesis" is sometimes used but this does not seem to be very helpful.) These are cases where phenotypically the individuals are female, having female internal and external genitalia and streak gonads which show ovarian rudiments. Urinary F.S.H. excretion is normal or increased. However, they are of XY karyotype.

The real nature of this group cannot yet be defined as only a few have been described since chromosomal analysis has been possible, so that chromatin negative patients may have been XO or XY or mosaics, while in other cases where the karyotype has been demonstrated, the gonad situation has not been confirmed by laparotomy.

The cases described by Swyer (1955), Hoffenberg and Jackson (1957), Harnden and Stewart (1959), de Grouchy and co-workers (1960) and Court Brown and co-workers (1964) appear to be of this type.

Bonnevie-Ullrich Syndrome

Ullrich (1930) described a syndrome affecting both sexes and probably determined by a single recessive gene, where the children may be indistinguishable from those with Turner's syndrome although skeletal anomalies appear to be more common and mental

impairment is rather constant. In addition neck-webbing is often unilateral, and even in the absence of webbing the head may be held on one side. The neck is usually very short and cranial nerve palsies are common. Follow up of girls with this syndrome indicates that they do not have ovarian dysfunction. Sexual development at puberty is normal. The sex chromosomes are XX and XY according to sex. (This is an oversimplified account, but probably approximates to the truth. For discussion see Polani (1962) and Lindsten (1963).)

Stein-Leventhal Syndrome

De Grouchy and co-workers (1961) describe briefly karyotypes of 3 cases of Stein-Leventhal syndrome previously reported by Netter (1961). One of the 3, as reported, seems more like ordinary ovarian dysgenesis and had an Xx karyotype. The other 2 resemble more closely the usual descriptions of the syndrome although neither had hirsutism. One was mosaic XX/Xx and the other was an XX/XXX mosaic. It is a little difficult to reconcile these karyotypes with those reported in another publication about what appear to be the same cases (Netter *et al.*, 1961). Leon and co-workers (1963) describe 2 typical cases, 1 having XX karyotype and the other having most blood leucocytes XX but about a third with 47 chromosomes, there being 2 X's and a small acrocentric, which the authors regard as a Y. The extra chromosome could, however, have been a No. 21 and the woman a mongol mosaic. It would be of interest to have detailed chromosomal reports on further typical cases of the syndrome such as those described in a recent review by Chamberlain and Wood (1964).

It seems rather unlikely that many cases of Stein-Leventhal syndrome are determined by chromosomal anomalies as many pairs of sisters have been described, e.g. Trace, Keaty and McCall (1960) and Evans and Riley (1960). Enlarged cystic ovaries have occurred in each of identical twins (Goldzieher and Green, 1962) but only one had the hirsutes and obesity so characteristic of the syndrome. It is possible that the condition is determined by a single recessive gene mutation.

Testicular Feminization

This term is used to describe individuals who have female external genitalia and body configuration, have undescended testes, and are of XY chromosome constitution, as first shown by Jacobs and co-workers (1959b). The testes are usually intra-abdominal or in the inguinal canal. A considerable proportion of women with

bilateral inguinal hernia prove to be examples of this syndrome and this is the usual way in which they came to attention in childhood. At puberty there is some development of female bodily form and breast development, but characteristically they have very scanty or absent pubic and axillary hair. Urinary pituitary gonadotrophins and 17-ketosteroids are usually at normal levels. Subjects often present with "primary amenorrhœa".

The external genitalia are feminine with normal clitoris, labia, introitus and hymen. The vagina is small and may end blindly at the beginning of the part developed from the Mullerian ducts. There is occasionally some incomplete development of uterus and tubes. The uterus, if present, is sometimes unicornuate.

A minority of cases show some ambiguity of the external genitalia with a large phallus, sometimes containing some urethra and sometimes with a urogenital sinus at its base.

The testes are usually small but are seldom, if ever, grossly abnormal on histology. A striking finding in the absence of masculinization is the presence of normal looking Leydig cells. Absence of androgens in the fœtus could explain the female external genitalia and the feminization at puberty might suggest that the circulating hormones are predominantly œstrogens. However, Griffiths, Grant and Whyte (1963) examined the synthesis of steroids *in vitro* by a slice of testicular tissue from a typical case of testicular feminization and concluded that there was no evidence to suggest that the endocrine disorder could be explained by inability to synthesize testosterone and there was no evidence of synthesis of œstrogens.

It is usually recommended that the testes should be removed, as malignant change occurs so frequently. Removal before puberty prevents breast enlargement and removal subsequently may be followed by slight menopausal symptoms.

This syndrome is probably determined by a single recessive gene on the X-chromosome. An interesting family is described by Puck, Robinson and Tjio (1960). More than one affected subject in a sibship has often been reported and sometimes maternal "aunts" have been affected. A full clinical description is given by Morris (1953).

True Agonadism or Overzier's Syndrome

The appearance of patients with this rare syndrome is similar to that in testicular feminization but they do not appear to have the characteristic absence of bodily hair. The external genitalia are female but only a vaginal introitus is present. No gonads can be

found. The early Mullerian and Woolfian ducts persisting side by side are the only signs of internal genitalia (Overzier and Linden, 1956). Overzier's first two cases were "sisters". A recent case of this type was described by Dewhurst, Payne and Blank (1963). So far all cases described have had male nuclear sex. XY chromosomes have been found in the three cases examined.

Multiple X Females

Probably females with this karyotype are not often referred to gynæcologists, but it so happened that the first reported XXX female (Jacobs *et al.*, 1959*a*) had secondary amenorrhœa. Scant and irregular periods started at the age of 14 and ceased, with menopausal signs, when the patient was 19 years old. She was a normal looking, if slightly underdeveloped, female. No mention was made of intellectual retardation. Subsequently a large number of cases has been reported. Most are of normal feminine appearance but are intellectually retarded. Most XXX females appear to menstruate normally and many have had offspring. So far their children have been either normal XX females or XY males (Stewart and Sanderson, 1960; Fraser *et al.*, 1960).

As yet the majority of cases have been identified in nuclear sexing of the new born retarded children or in vaginal smears of apparently normal women by reason of their being more than one sex chromatin body in cells. Close (1963) reports two such subjects who were discovered because of double Barr bodies in course of screening 900 vaginal smears at a pre-cancer clinic.

Several instances of XXXX karyotype (e.g. Barr and Carr, 1960) and one of XXXXX (Kesaree and Woolley, 1963) have been described. In none of these has pregnancy been reported. With the exception of more severe mental retardation subjects appear to be indistinguishable from XXX females.

"Intersex" Anomalies of Genitalia

Subjects presenting because of ambiguous external genitalia constitute a group varying enormously in morphology, status of gonads and sex chromosome constitution.

Masculinization of the female and precocious development in the male determined by androgens of adrenal origin, do not often present diagnostic problems and the karyotypes are concordant with the phenotypic sex. This diagnosis is suggested by virilization and may be confirmed by endocrine studies.

The "true hermaphrodites" having both ovarian and testicular tissue have a big morphological variation, and may or may not show some ambiguity of external genitalia.

Congenital Adrenal Hyperplasias

The congenital adrenal hyperplasias account for a considerable proportion of female infants presenting with some virilization. They appear to be determined by a series of autosomal recessive gene mutations. Affected females with male sibs having precocious puberty have frequently been described, as has consanguinity in parents.

It is difficult to know how many variants there are but as knowledge accumulates it is becoming clear that different specific defects in hydrocortisone biosynthesis determine relatively specific clinical pictures although inevitably they vary in the two sexes. Tomkins and McGuire (1960) recognize four types characterized by virilization only, virilization and adreno-cortical insufficiency, virilization and hypertension and virilization with adreno-cortical insufficiency and hypertension, but there are others outlined in brief by Hamilton and Brush (1964) and they describe 4 cases each probably associated with anomaly of a different enzyme concerned with steps in steroid synthesis from cholesterol. Such findings are rather suggestive of the homozygous effect of a series of alleles at a particular functional gene locus but entirely different gene loci may be involved. Endocrine aspects are well reviewed by Steinbeck (1963). Regarding the "intersex" aspects of these conditions there is seldom serious doubt about the phenotypic sex, although occasional females may be classed as males at birth or labelled "female pseudohermaphrodites", when the phallus is greatly enlarged, often with a urogenital sinus at its base. The labia minora are vestigial and the labia majora which may be rugose are sometimes fused, but the uterus, tubes and ovaries will be found to be normal. In males hypospadias may sometimes be associated with precocious sexual development.

As the children grow, virilization becomes more marked but in milder cases menarche may occur in females, and in the excess sodium loss types treatment with deoxycorticosterone and cortisone has permitted pregnancy (Gans and Ser, 1959). At the most elementary level the diagnosis rests on concordant phenotypic and sex chromosome karyotypic sex and the excess 17-ketosteroid excretion.

Congenital Adrenal Insufficiency with Lipoid Cortical Hyperplasia

This rare condition was first reported in female infants (Sandison, 1955). Since then cases have been described in males (see review by Prader and Siebenmann, 1958). The children often die early from ACTH resistant cortical insufficiency. Subjects have been described with female external genitalia, no internal genitalia but intra-abdominal testes. The chromosomal situation has not so far been investigated but in one boy no sex chromatin bodies were found (Prader and Siebenmann, 1958). It will probably prove that most cases of this syndrome are determined by single autosomal recessive genes.

Syndromes Determined by Exposure of the Fœtus to Androgenizing Hormones

Cases where ovarian tumours appear to have determined masculinization of a female fœtus are very rare. No chromosomal anomalies have been reported. Many cases of masculinization of the fœtus following exhibition of progestogens with androgenic properties to the mother during pregnancy have been described. In the cases investigated chromosomal and phenotypic sex have been concordant. As in the case of congenital adrenal hyperplasia the main effeets are on the external genitalia as opposed to uteri and tubes. There are similarly some reports of concordant chromosomal and phenotypic sex in girls showing enlarged clitoris and liabial fusion following therapy to the mother during pregnancy with steriods having progestational activity. (For a review of these exogenous cases see Wilkins, 1960.)

"True Hermaphrodites"

Only about 100 cases of patients having both male and female gonad tissue have been described. However, the condition may be commoner than this suggests as only in a proportion of cases of ambiguous sex is laparotomy performed and it is impossible to be sure at operation that small nests of ovarian or testicular tissue are absent. The gonads of the two sexes may be separate or combined ("ovotestes"). Separate gonads are often on either side of the body

and often the development of the internal genitalia follow the sex of the gonad on the same side.

Testes may be in a scrotum or the inguinal canal and are often greatly atrophied. Ovaries are seldom ectopic and often relatively normal in appearance, but they may be atrophied or replaced by fibrous tissue to the degree seen in ovarian dysgenesis. Ovotestes often appear like undescended testes and the ovarian and testicular sections are frequently separated by a fibrous septum. They may be unilateral or bilateral, and inguinal or abdominal. Only serial sections may reveal their true nature. The external genitalia are almost invariably malformed and the degree and types of anomaly vary considerably, overlapping with those determined by these developmental anomalies of the urogenital ridge of unknown origin discussed below.

All degrees of intermediate development of phallus and labio-scrotal folds are seen, and the rudimentary opening or vestibule of the vagina frequently communicates with the urethra. The vagina may only be a slight depression or may end blindly at the junction with the Mullerian portion. The latter may communicate with the bladder. A more or less normal vagina may be present even with a large phallus, and the urethra may be contained in the phallus with a ventral or even occasionally a terminal opening. Almost any variant of unilateral or bilateral mal-development of structures derived from the Mullerian ducts may be seen.

Body configuration, breast development and body hair are extremely variable. Gynandomorphism, with one side of the body male in appearance and the other female, as seen in *Drosophila*, occurred in a case described by Brachetto-Brian, Grimaldi and Tachella Costa (1943). Endocrine assays are not of much help in diagnosis. Menstruation may occur from vaginal orifice or periodic hæmaturia may occur. Where the anatomy permits and some testis tissue is functional, spermatozoa in seminal fluid may be found. The nuclear sex may be male or female, usually the latter.

Only in a few cases have chromosomal studies been carried out. Most of the subjects appear to be of XX karyotype (e.g. Harnden and Armstrong, 1959; de Assis *et al.*, 1960; Gordon *et al.*, 1960; Ferguson-Smith, Johnston and Weinberg, 1960). However, XO karyotype (Atkins and Engel, 1962), XY/XO (Hirschhorn, Decker and Cooper, 1960), XX/XY (or ? XX/Xx) (Waxman *et al.*, 1962) and XX/XXX (Ferguson-Smith, Johnston and Weinberg, 1960) have been described. In a remarkable case with left ovotestis and right primitive testis the mosaic karyotype was XX/XXY/XXYYY

(Fraccaro *et al.*, 1962). In another with a testis on one side and an ovary on the other the karyotype was XX/XXYY (Blank *et al.*, 1964). It has been suggested, but is unproven and unlikely, that most true hermaphrodites are really mosaics having one cell line which includes a Y chromosome. Several cases of two true herm-aphrodites in the same family have been reported so that it is possible that some cases are genetically determined but no chromo-somal studies have been carried out in such cases.

Non-concordance of Gonadal and Karyotypic Sex

Patients Who Have Testes but are of XX Karyotype

Shah and co-workers (1961) described a patient apparently female but with some ambiguous features of external genitalia. She had only testes but was chromatin positive on buccal smear and was shown to have XX karyotypes in skin fibroblast cells. No other cases have been described and it could be that there was undiscovered mosaicism with an XY cell line.

Recently, however, Therkelsen (1964) has described a man who was investigated because his marriage was infertile. He appeared to be a normal male with penis and smallish testes. 17-ketosteroid excretion was slightly lowered but 17-ketogenic steroids, œstrogens and pituitary gonadotrophins were at normal levels. On biopsy no germ cells, only Sertoli cells were found in the testicular tubules and Leydig cells were hypoplastic. The karyotypes of cells from skin and both testes was 46 XX in a large number of cells examined and in the few aberrant cells found there was no suggestion of a Y chromosome. The testicular histology in this case is similar to that described by Del Castillo, Trabucco and Balze (1947).

Patients who have Ovaries but are of XY Karyotype

The other possibility, namely, XY karyotype in presence of func-tioning ovarian gonads has not been conclusively demonstrated although Ashley and Jones (1958) and others have shown patients with some phallic enlargement but with uterus and ovaries only to be chromatin negative in buccal smear cells. These cases, sometimes called sex reversal, are to be distinguished from those mentioned earlier where there is ovarian dysgenesis associated with an XY karyotype, but what, if any, is the relationship between the two types is not yet known. It is difficult to be certain of this phenomenon of so-called sex reversal as, on the one hand, it is always possible

that an apparent XY individual has undiscovered XX cell lines, and on the other it is difficult to be sure that there are no nests of testicular tissue which remain undiscovered at laparotomy.

XO/XY Mosaicism

The occurrence of XO/XY mosaicism has already been mentioned as associated with ovarian dysgenesis and true hermaphroditism. A bewildering variety of other clinical associations has been described. Jacobs and co-workers (1961) have reported two phenotypic females with underdeveloped genitalia and streak gonads and similar cases have since been reported by Judge and co-workers (1962) and others. Willemse, van Brink and Los (1962) describe a female with enlarged clitoris and hirsutism who had a right streak gonad, and in the usual ovary position on the left a gonad which was a testis. A somewhat similar case is described by Blank, Bishop and Caley (1960). A girl of 9 years reported by Mellman and co-workers (1963) had enlarged clitoris and female internal genitalia but the intra-abdominal gonads proved to be testes. In contrast, Ferrier and co-workers (1963) report a male with normal penis and two rather small testes in a normal scrotum. Biopsy of one testis showed only testicular material but no spermatogenesis.

Conen and Erkman (1963) describe another "female" subject with negative buccal smear and XO/XY karyotype. One gonad was in the left side of a bifid scrotum and the other in a right inguinal hernia. She had a large phallus with the urethral opening at its base and a vagina, uterus and tubes. Ferrier and co-workers (1962) describe a male of superior intelligence having normal male hair distribution, severe hypospadias, undescended testes, uterus and tubes.

In 2 reported cases neoplasms have been associated. In the case of Robinson, Priest and Bigler (1964) a stunted female with some masculinization of external genitalia and rudimentary internal genitalia had pelvic gonads which were part testes and part "gonadoblastoma" which showed no ovarian follicular elements. In a male with hypospadias and bifid scrotum reported by Lewis, Mitchell and Foss (1963) a malignant seminoma of testes was followed 16 years later by an adenocarcinoma of body of uterus.

Only time and experience will illuminate this complex pattern. The variability is no doubt in part determined by differing proportions of the two cell lines in different tissues and by failure to recognize true hermaphrodites at laparotomy.

Malformations of Genitalia and Other Structures Developed from the Urogenital Ridge Not Associated with Karyotype Anomalies

The majority of macroscopic developmental disorders in the body are not known to be associated with chromosomal abnormalities or with single gene mutations. In most the intra-uterine environment appears to be of major ætiological importance but there is also frequently evidence suggesting a predisposing contribution of the embryo. The nature of this genetical contribution is ill-understood, but in most cases it appears to be determined by many different genes.

When these developmental disorders affect the genitalia they may mimic or indeed be identical with some of those previously described as associated with karyotypic anomalies. However, a majority appear to be part of a general instability of development of structures derived from the urogenital ridge so that there are associated urinary tract malformations. In many cases the true situation will only be clear when karyotype analysis and histology of gonads following laparotomy has been carried out.

Perhaps one of the simplest malformations of this type is hypospadias and as is well known occasional males with severe hypospadias are classed as females at birth and present at puberty with deepening voice, hirsutism and "amenorrhœa".

In other cases the external genitalia are completely ambiguous, there being a persistent urogenital sinus and a great variety of malformations with communication between vagina, uterus and bladder. In less degrees there may be a large phallus, sometimes with urethral opening at its base, and a rudimentary introitus or vagina. There is sometimes difficulty in distinguishing these cases from extreme degrees of hypospadias.

In the great majority of the above types of patients the gonadal sex is not in doubt and is concordant with the chromosomal sex. However, some cannot be distinguished clinically, or by nuclear sexing, and only chromosomal analysis and laparotomy with gonad biopsy will reveal the true situation.

Many studies have confirmed the presence of ovaries and normal XX karyotype in females with the various degrees of duplication of the uterus, cervix and vagina. As is well known, such patients often have urinary tract anomalies of a wide variety. Susceptibility to unstable urogenital ridge development resulting in these disorders often appears to be inherited by daughter from mother (for review see Wilson and Harris, 1962).

Those well developed girls with rudimentary or absent vagina and absent uterus have in the writer's experience all proved to have normal XX karyotypes. No cases with discordant karyotypes have been reported.

Indications for Nuclear Sexing and Chromosomal Analysis

From the foregoing it is rather clear that any patients referred to gynæcologists with some ambiguity of genitalia or with primary amenorrhœa may prove to have an abnormal sex chromosome karyotype. It would be a formidable undertaking to organize chromosome studies on all such patients, but a majority of karyotype anomalies will be suggested by adequate sex chromatin studies and these should normally precede collection of specimens for culture and chromosomal analysis.

A knowledge of the karyotype is in many cases of practical importance in that the gonadal situation may be inferred and the need for laparotomy assessed. Thus females with primary amenorrhœa, normal urinary F.S.H. output and XO karyotype are virtually certain to have streak gonads, and laparotomy is not necessary. In contrast in a female with an XY karyotype, or a mosaic which includes an XY it may be considered important to search for and remove any testicular material.

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GLOSSARY

Terms Descriptive of Normal Chromosomes

Karyotype

The chromosomal constitution of an individual or of a cell.

Euploid—Aneuploid

The *haploid* number of a species is the number of chromosomes in normal gametes—in man 23.

The *diploid* number is that twice as large characteristic of normal somatic cells—in man therefore 46.

Any chromosome number which is a simple multiple of the normal haploid number is termed euploid, thus, haploid—23, diploid—46, triploid—69 or tetraploid—92, are all euploid numbers. Any departure from this determined by a missing or extra chromosome is termed aneuploid.

Autosomes

These are the chromosomes other than the sex chromosomes.

Centromere

A point, perhaps a specialized gene on a chromosome which stains less deeply than the rest of the chromosome with nucleic acid stains. When chromosomes divide to form chromatids (or daughter chromosomes) the last point of separation is at the centromere. An intact centromere is necessary for accurate migration of the chromatids to opposite poles to form the daughter nuclei when a cell divides.

Satellites

These are excretions of Feulgen staining material (indicating presence of deoxyribose nucleic acid) attached to chromosomes, in man usually to the ends of acrocentric chromosomes.

Acrocentric

Chromosomes are those which only have one major arm, the arm on the other side of the centromere being rudimentary and difficult to distinguish so that superficially they appear to have only one arm (e.g. pair 16–18 and 21 and 22).

Metacentric

Chromosomes are those having two distinct arms. The third chromosome pair is the only one with apparently equal arms. Sometimes chromosomes with the centromere near one end are termed sub-metacentric.

Monosomy, Trisomy, Tetrasomy, etc.

This is where, in respect of a specified chromosome instead of the usual pair being present in a cell there are one, three, four, etc., e.g. trisomy 21 in mongolism.

Non-disjunction

The process of abnormal cell division whereby the daughter cells receive unequal numbers of chromosomes. The term is often used in a more specialized sense by cytologists to indicate one of several mechanisms by which the unequal distribution of chromosomes occurs.

Mosaicism

In respect of chromosomes this denotes a situation where an individual has two or more cell lines or clones of cells of different karyotypes. These derive from non-disjunction or chromosome loss in cleavage divisions of the zygote.

Abnormal Chromosomes

Deletion

This is loss of a portion of a chromosome following breakage. A fragment without a centromere gets "lost" in a cell division and is absorbed. The deletion may be terminal following a single break or interstitial if two breaks occur, the intervening portion is lost and the terminal portion rejoins the main chromosomes.

Isochromosome

A chromosome formed by two chromatid arms, the other two being lost. In cell division instead of the two chromatids separating, one pair of arms is lost and a single new chromosome consisting of the other two arms joined at the centromere passes to one daughter cell. An isochromosome has therefore equal arms and a median position of the centromere.

Ring Chromosome

A chromosome which has assumed the form of a ring by joining of two broken ends. If this ring includes the centromere, the ring chromosome may divide in mitosis and pass to daughter cells.

Translocation

This means attachment of a part or possibly sometimes a whole chromosome to another. Thus 21–15 translocation indicates that a No. 21 chromosome is attached to a No. 15. Reciprocal translocation means interchange of portions of two chromosomes which may be homologous or non-homologous chromosomes. Thus, an example is given in the text of such an interchange between chromosomes Nos. 3 and a 6–x–12 group.

Meiosis and Words Used in the Text Descriptive of Stages in Terms of Sequence and of Chromosome Structure and Relationships in the First Meiotic Division

Meiosis

The changes which occur whereby the early diploid germ cells divide to form later stage haploid germ cells which mature without further cell divisions to form gametes. The first and second meiotic divisions are described in the text under spermatogenesis and oogenesis.

Stages in First Meiotic Division Mentioned in Text

Prophase

The initial stage in cell division during which the chromosomes, not detectable as structures in interphase, become visible.

Pachytene. The stage in meiotic prophase when the paired chromosomes split longitudinally and lie closely opposed. Chiasmata, believed to be associated with exchange of chromosomal material

(crossing over) take place between chromatids of opposite pairs and these hold the pair together until just before metaphase.

Diplotene. The stage of meiosis following pachytene when the pairs of chromatids move apart but remain attached by chiasmata.

Dictyate. A late stage in diplotene. It is believed that in human ova the chromosomes remain in this stage in the first meiotic division from shortly after birth until shortly before ovulation.

Metaphase

The stage at which the chromatid pairs (each still held together at the centromere) finally separate and become arranged on the metaphase plate (see text).

Anaphase

This stage begins when the chromatids finally separate at the centromere and one of each pair starts to move towards the opposite pole of the spindle. The stage lasts until the daughter nuclei are reconstituted and the chromosomes begin to elongate and cease to be detectable (telophase).

Symbols and Conventions Used in Describing Karyotypes

Homologous pairs of chromosomes are identified so: XX or XY or 21 . 21, indicating that these are the two of the designated pair. Similarly, if there is aneuploidy with three or more homologous chromosomes they are shown XXX, or XXXX or XXYY, etc. Absence of one of a pair of chromosomes is indicated by O. Thus, XO indicates that there is one X chromosome only and no Y.

The nature of mosaicism is indicated by the successive karyotypes in respect of homologous chromosomes separated by an oblique. Thus, XX/XY or 46/47 indicates that the individual has some cells of each constitution.

Abnormal chromosomes structure. A small symbol is used to indicate *a missing portion of a chromosome*. Thus, Xx or Xy indicate respectively that the cells had one normal X and one with a part missing, or a normal X and a Y with a part missing.

An *isochromosome* of X is indicated by X(i). (r) is used to indicate *ring chromosome*, thus X(r).

General Genetic Terms

Genotype

The general genetical constitution of an individual or the situation in respect of a specific pair of homologous genes.

Phenotype

The somatic or bodily manifestation of the genotype or karyotype.

Pronucleus

The nucleus (haploid) of an ovum or sperm. The term is used particularly when both male and female pronuclei lie in the cytoplasm of the ovum in fertilization but have not yet joined.

Syngamy

The process of fusion of male and female germ cells to form the zygote. It is sometimes used more specifically to note the joining of the nuclei.

APPENDIX II
SPECIMENS FOR NUCLEAR SEXING

Any technique suitable for taking smears for other exfoliative cytology tests may be used for buccal or preferably vaginal smears. The use of a flat ended metal spatula is recommended. It is helpful if the mucosa is first swabbed lightly with a dry gauze which gets rid of excess secretion and many bacteria. The material from the spatula should be smeared on to a clean microscope slide, another placed on top, the two gently pressed together and then slid apart as in making blood films.

The smears must not be allowed to dry, but must be fixed at once by immersion in a 50% industrial spirit 50% ether mixture. They must remain there for 2 hours and then be air dried. In this condition they will keep indefinitely for staining. The staining methods used vary. The one in use in this laboratory is to hydrolize with N/10 HCl and stain with Cresyl Fast Violet. The staining is then differentiated with alcohol and when ready brought through alcohol to Xylol and then a coverslip mounted.

APPENDIX III
SPECIMENS FOR CHROMOSOMAL ANALYSIS

Blood

This is for most purposes a specimen of choice and the most satisfactory specimen is of a few drops of blood taken from a skin prick by capillary pipette and placed directly in a buffered amino acid solution. The specimen should reach the laboratory as soon as

possible. The great majority are satisfactory up to 24 hours but thereafter the failure rates rise rapidly. Alternatively 100 ml. of whole blood received with minimum of frothing into a sterile standard ontainer with 0·1 ml. of 20 mg. % heparin is a satisfactory specimen but it must be received in the laboratory within two hours of collection.

Unfortunately for as yet unexplained causes there are still failures with specimens in all laboratories. Satisfactory mitoses may not occur. Spreading of chromosomes from cells in mitoses may not be sufficiently good to give adequate numbers of well spread chromosomes. It is unlikely that any laboratory achieves more than 90% success. Unknown factors in the technique of these short term leucocyte cultures seem to determine unexplained runs of failures in all laboratories. Various micro-techniques have been developed but there are so many different techniques in use that the laboratory to which specimens are to be sent should be consulted.

From reception of the specimen about 4 days are required to complete culture and preparation of slides. At least 2 days will elapse thereafter before a report can be given, even if the laboratory has no back-log of specimens, because analysis of cells, even to say a specimen is probably normal, takes a minimum of $1\frac{1}{2}$ hours of microscopy. Photographs of euploid and aneuploid cells followed by matching of chromosomes takes time and it is usually necessary to go back and look at the slides in the light of the photographs. In difficult cases more microscopy and many more photographs may be required and repeat specimens may be necessary to be sure that anomalies seen did not arise in culture.

Skin

The alternative routine specimen is skin. This need only be a very small superficial specimen so long as it is deep enough to reach the corium or true skin. The simplest way to obtain a specimen is clean the skin with ether, allow to dry and to then pinch a small fold of skin between the blades of a pair of dissecting forceps. A thin slice is then taken off with a sharp sterile razor blade. There should just be oozing where the tops of the vascular corium ridges have been removed. The procedure is no more painful than collection of a specimen of venous blood. The oozing blood may be taken for a micro-specimen.

The specimen should be dropped immediately into a buffered amino acid mixture such as "199" with a little broad spectrum antibiotic. Specimens so collected may be kept at room temperature

for many hours or sent by post. In emergency specimens may be sent in sterile normal saline. Depending on the technique used such specimens on culture and sub-culture would take 3 to 6 weeks to yield appropriate slides with mitosis.

Other Tissues

The same procedure may be used for specimens of any tissue in the body taken at operation or from cadavers. Usually specimens taken up to 48 hours after death will grow. It is helpful to have specimens from internal tissues from autopsy as it is easier to ensure reasonable sterility.

FERTILITY AND STERILITY

The increase in world population in 1964 is estimated at 60,000,000 and those two great compensating enemies of mankind—war and pestilence—though not conquered, are more in subjection than ever before. Where the standards of living are lowest the birth rate is highest, so that adequate food and population control have become two of the world's major problems. Recognition of their importance has grown with an increasing awareness of the political and social implications of poverty, famine, and ignorance. With issues of such magnitude thought must precede action, and planning on a gigantic scale will be necessary to achieve some degree of equilibrium. A significant advance indicating new freedom of thinking has been the review of contraception by two such entirely different bodies as the Vatican Council on the one hand and the Consumers' Association of Great Britain on the other. The latter has issued its report, but the views of the former will be of much greater importance to mankind and are still awaited.

The wishes and desires of individuals, as opposed to the edicts of their leaders, must ultimately govern any effective solution. In over-populated areas there are women desperately anxious to have babies, and in more favoured parts of the earth there are fertile women fearful of unwanted pregnancy, although an increased population is essential to survival. Any review of this subject must include reference to both aspects, and recent advances, important both to those who desire pregnancy and to those who do not, are considered in the following pages.
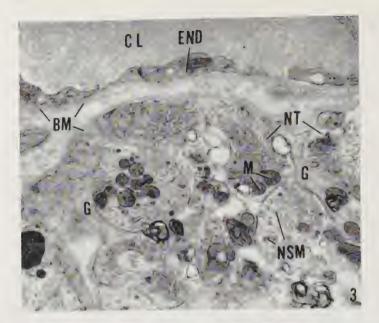
Developments have centred mainly round a better understanding of the physiology of human ovulation with knowledge of how to induce or prevent it. By correlating their action with molecular structure chemists are synthesizing new and powerful preparations and making dramatic contributions to knowledge and therapy. The influence of mind over body, and body over mind, is nowhere better illustrated than in recent research into the physiology and control of the anterior pituitary gland.

Pituitary Function

A medical student in Bucharest observed that the anterior pituitary gland was connected by a leash of vessels to the median eminence of the hypothalmus. This young man, Gregory Popa, later worked in London with Dr. Fielding and published the first description of the pituitary portal system (Popa and Fielding, 1930, 1932). Green (1951) demonstrated that this was common among vertebrates and that blood flowed from the median eminence to the anterior pituitary gland. Unlike the posterior pituitary the anterior has no direct nerve connection with the brain and Harris (1937) and Green and Harris (1947) advanced the theory of hypo- thalamic control through a neurohumoral mechanism. Their concept was that chemical substances liberated by stimulation of nerve endings in the median eminence reached the anterior pituitary gland through the portal vessels. Bargmann (1958) and Knowles (1963) demonstrated neurosecretion in the posterior pituitary by nerve stimulation through a direct pathway. The vascular connec- tion between median eminence and anterior pituitary is all-important. For example, the gland ceased to function when the pituitary stalk was severed, but anterior lobe activity returned when vessels regenerated from the median eminence although there was no recovery of the posterior lobe. If a transplanted gland from a new- born animal is correctly placed in relation to the hypothalamus of the hypophysectomized mother, vessels grow into it from the median eminence, and ovarian and thyroid function are regained, but the gland atrophies if oiled paper is inserted between it and the hypothalamus.

Harris (1964) studied the rat median eminence by electron- microscopy and demonstrated endothelial capillary windows communicating with perivascular spaces close to nerve terminals with synaptic vesicles and more solid, larger, opaque masses of neurosecretory material (Fig. 50). Extracts of the median eminence of cattle, rats, cats and monkeys were applied directly to the anterior pituitary gland of the rabbit, 0·1 ml. every 2 hours. Ovulation occurred 6 times in 99 controls when substances such as adrenalin were injected, but in 55 of 96 experiments when median eminence extract was used.

It is now known that these extracts contain more than one acti- vating substance. Guillemin (1963) isolated a substance (CRF), the corticotrophic releasing factor, which stimulates the anterior pituitary to release adrenocorticotrophic hormone. A luteinizing
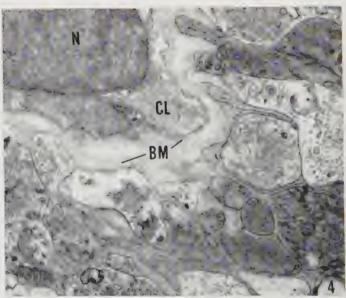
FIG. 50. Electron micrograph of the median eminence of a female rabbit at œstrus. Note the capillary lumen (CL), the fenestrated endothelium (END) and the surrounding basement membrane (BM). Nerve terminations (NT) are visible, containing mitochondria (M), neurosecretory material (NSM) and many small synaptic vesicles; glial cell processes (G) are also seen. (Harris.)

hormone-releasing factor (LRF) was demonstrated by Harris (1961), by McCann *et al.* (1961), and Courrier *et al.* (1961), who also demonstrated a thyrotrophic hormone-releasing factor (TRF). These studies confirm that a number of chemical substances specifically activate the anterior pituitary gland. Harris (1964) thinks they are polypeptides with a molecular weight of approximately 1,000 and that possibly they are not species specific. When these substances can be synthesized it may be possible to stimulate the production of antibodies and the implications of this would be far reaching in many fields of medicine, not least in population control.

Harris (1948, 1950) demonstrated that electrical stimulation of various hypothalamic areas produced different effects. The tuberal and posterior regions liberated luteinizing hormone and adrenocorticotrophic hormone, while the supraoptic area released thyrotrophic hormone. The secretion of follicle-stimulating hormone, growth hormone, and lactogenic hormone has not been studied in detail although damage to the anterior hypothalamus is followed by release of follicle-stimulating hormone under conditions in which it would not normally occur, as for example in immature female rats and in female ferrets when normally in sexual quiescence (Donovan *et al.*, 1959). Similarly, Haun and Sawyer (1961) increased the production of lactogenic hormone by damaging selected hypothalamic areas. These experiments suggest that the lesions interfere with a normal inhibiting influence over the secretion of hormones and support the view that the hypothalamus exercises control over the anterior pituitary both by exciting and inhibiting its action. It is now possible to outline in the hypothalamus, areas associated with the secretion of specific hormones just as areas of the cerebral cortex are identified with specific muscular action. Selective action of the anterior pituitary gland is manifested clinically by the excessive release of lactogenic hormone in the Chiari-Frommel and Argonz-del-Castillo syndromes. Galactorrhœa can be caused by a pituitary tumour, usually a chromophobe adenoma, and may be associated with small ones causing no enlargement of the sella. It can also occur in the absence of tumours as described by Bercovici and Ehrenfeld (1963) who reviewed 71 patients suffering from this condition.

Many areas of the brain apart from the hypothalamus can influence anterior pituitary function. Klüver and Bartelmez (1951) studied the effect of the temporal lobes of monkeys on gonadotrophin secretion, and reticular formation in the brain stem has also been implicated in the release of gonadotrophins and ACTH. Central

nervous system control of the anterior pituitary is governed by a feed-back mechanism which regulates activity according to the concentration of circulating hormone produced by the target gland, be it ovary, thyroid, or adrenal. These hormones also exercise a powerful influence over behaviour as illustrated by the clinical manifestations of both hyper- and hypothyroidism. An increased circulation of gonadol steroids affects the central nervous system of lower animals, and is the physiological explanation for certain patterns of human behaviour picturesquely described by the poets. Michael (1964) demonstrated the effect on a cat's behaviour of combined hypothalamic damage and hormone stimulation resulting from an œstrogenic implant in the lateral hypothalamus.

Harris (1964) considers there is a fundamental difference in the central nervous system of the male and female. In the latter the hypothalamus controls the rhythmical release of gonadotrophins leading to follicular maturation and cyclical ovulation, whereas in the male gonadotrophin secretion is steady and controls testicular activity. Ovarian transplants in the eye of a male animal revealed constant follicular ripening with no cyclical activity. The same occurred with transplants in a castrated male adult rat, whereas with a normal female, and one ovariectomized when adult, rhythmic changes occurred. If the female was treated with testosterone after birth characteristic cyclical changes did not occur, and the male pattern was seen, but if the male was castrated at birth the absence of testosterone resulted in cyclical changes with corpus luteum formation characteristic of the female. The adult sexual behaviour of animals treated in this way was tested and the results supported the concept of a basic difference in the behaviour of the male and female central nervous system. Harris summarized these findings by stating that the male type of central nervous system develops if testosterone is present and the female type if it is absent.

Species Specificity

Smith and Engle (1927) and Zondek and Aschheim (1927) brilliantly demonstrated that the anterior pituitary gland controlled reproductive function. Since failure to ovulate was first recognized as a cause of infertility efforts have been made to induce ovulation by hormones, including chorionic gonadotrophin as reported by Zondek (1928), Stewart et al. (1948), Kenny and Daley (1940) and others. The weight of evidence failed to conform that this was effec-

tive, although Kenny and Daley, and Bergman (1958) believed that it was. Thyroid, œstrogenic compounds, and cortisone were also tested. Buxton (1953) explained the failure of gonadotrophins when he demonstrated species specificity in the pituitary ovarian relationship. Van Wagenen and Simpson (1957) and Gemzell et al. (1958, 1960) confirmed this by inducing ovulation in the pre-pubertal and adult monkey, and in women with amenorrhœa, with homologous pituitary extracts. Menstruation and ovulation returned in 29 of 40 women treated by Gemzell, and 8 of the 11 failures occurred in patients with either no ovarian tissue or rudimentary ovaries. A marked increase of corticosteroids and 17 ketosteroids was demonstrated in the other 3.

Clinical Results

Buxton and Herrmann (1961) tested various combinations of human pituitary gonadotrophin and human chorionic gonadotrophin (HPG and HCG) on 9 patients, 8 of whom had amenorrhœa. The other menstruated normally. After skin testing for sensitivity, they finally selected 10 mg. of HPG twice daily for 4 days followed by a further 10 mg. plus 8,000 units of HCG twice daily for 4 days. The injections caused some discomfort for 6–8 hours and ovarian enlargement, sometimes to 3 or 4 times the normal size. Culdoscopy and laparotomy twice confirmed multiple ovulations. This technique was used successfully 5 times. Buxton et al. (1963) reported 28 courses of HPG–HCG therapy given to 11 patients with hypogonadotrophic amenorrhœa or anovulation, diagnosed from the history, examination, gonadotrophin excretion, thyroid studies, X-ray of sella turcica, evaluation of visual fields and baseline steroid excretion levels. Each patient had a preliminary trial on HCG (only one ovulated), followed by an 8-day course of HPG alone for 4 days and HPG and HCG for 4 days. The dose of HPG, equivalent to 20 mg. Armour Standard 264-151X FSH, was considered to contain $10-15\%$ LH (luteinizing hormone) although the amount may have been larger. Progestational activity due to ovulation occurred a variable number of days after treatment and consisted of basal temperature rise, disappearance of ferning in cervical mucus, endometrial secretory changes, and in one case pregnancy. Buxton quotes Gemzell as stating that 20 pregnancies occurred in 50 previously sterile women after ovulation was induced. Ten went to term and 7 pregnancies were multiple, but 3 of these

patients aborted. In Buxton's series, a 26 year old patient conceived after 10 years of amenorrhœa, and pregnancy also occurred in a woman who was given FSH menopausal urine extract (Perganol) and HCG. Steroid excretion studies confirmed that human gonadotrophin containing FSH and LH is necessary to trigger œstrogen and progesterone production by the ovary, and presumably to induce ovulation.

Gross ovarian enlargement and high levels of steroid excretion following the administration of human FSH indicate the maturation of many follicles, whereas only one usually reaches full development in a spontaneous cycle. When multiple matured follicles, stimulated by exogenous homologous gonadotrophin, were exposed to luteinizing hormone, ovulation resulted in several. Whether the ova were normal is questionable in view of the relatively small number of pregnancies which occurred. It appears that large doses of FSH are necessary to initiate follicle growth, and the time required for ovulation after the administration of human chorionic gonadotrophin is remarkably constant at about 10 hours.

Crooke *et al.* (1963, 1964) studied the effect of pituitary and urinary follicle-stimulating hormones and chorionic gonadotrophin on patients with idiopathic secondary amenorrhœa, atrophied ovaries and uteri, and a reduced gonadotrophin excretion. The response to human pituitary or urinary follicle-stimulating hormone, followed by chorionic gonadotrophin, was assessed by the excretion of œstriol, estimated by a modification of the method reported by Brown (1955), and pregnanediol, determined by the method of Klopper, Mitchie and Brown (1955). The dose of follicle-stimulating hormone was measured in milligram equivalents of the International Reference Preparation of Human Menopausal Gonadotrophin (IRP-HMG). Crooke (1963) concluded that:

1. Patients vary in their sensitivity to these hormones.
2. Preparations containing the smallest amount of luteinizing hormone are the most effective.
3. The response is in proportion to the total dose of follicle-stimulating hormone, and equal daily doses are more effective than increasing ones.
4. The best results are obtained when a large dose of chorionic gonadotrophin is given in a single injection after the last dose of follicle-stimulating hormone.

An unexpected finding was poor correlation between steroid excretion and the amount of menstrual bleeding. A most important

aspect of the trial was that 4 of the 5 patients studied, conceived during treatment.

In 1964 the same authors published the results of a further study of 4 additional patients with idiopathic secondary amenorrhœa. Their ages were 25, 24, 28 and 30 and the period of amenorrhœa varied from 4 to 13 years. Two of the patients previously had regular cycles of 4/28 and 5/30 day type, whereas the other 2 had been irregular and menstruation failed gradually in these. Culdoscopy confirmed that ovaries were small and without cysts in 2 patients and normal in size but without cysts in one. They were not defined in the fourth. The largest uterus measured 6·25 cm. and 2 were 5 cm. in length. There was no endometrium in 2, a scanty but proliferative type histologically in one, and it was scanty and inactive in the other. The dose of HPG was either 2,400 units or 4,000 units, and of HCG 12,000 or 24,000 units. The total dose of HPG varied from 5,600 to 7,200 units and the schedule advised was to administer this in equal divided doses on days 1, 5 and 8, followed by HCG 12,000 or 24,000 units on day 10. The 3 patients to whom 24,000 units of chorionic gonadotrophin were given on day 10 after the preliminary administration of IRP-HMG in doses of 7,200 mg., 6,600 mg. and 6,000 mg. had pregnanediol excretions on the 17th day of 21 mg., 12 mg. and 4·9 mg. and all 3 conceived. There was no multiple pregnancy. Of 9 women treated for secondary amenorrhœa, 1 withdrew from the trials because of dysmenorrhœa when menstruation returned, 7 conceived. Their conclusions were:

1. A greater excretion of pregnanediol occurs when human chorionic gonadotrophin is injected on day 10 rather than day 8.
2. Higher doses of human chorionic gonadotrophin are more effective when given after high doses of follicle stimulating hormone.
3. A more normal pattern of steroid excretion is obtained with larger doses of each.
4. The timing of chorionic gonadotrophin administration is important and the best results follow when it is given 2 days after the last dose of follicle-stimulating hormone.

The effect was studied of gonadotrophins on a patient with Simmonds Disease following the removal of a pituitary tumour. Anovulatory bleeding occurred 4 times in 9 months.

Human pituitary gonadotrophin is expensive and difficult to obtain but its action in carefully selected patients is dramatic.

Perganol is produced in Italy from the urine of menopausal women and now species specificity has been proven there will be increasing demands for these hormones. Meanwhile research into the nature of the polypeptide activator of the anterior pituitary gland continues and may provide readily available and cheaper substitutes.

The need to avoid stimulating ovaries excessively by gonadotrophins was emphasized by Béclère (1960) in an analysis of 26 patients requiring emergency laparotomy. One died. Total or partial removal of large ovaries was commonly performed, although it is difficult to understand why. Excessive ovarian response to gonadotrophin stimulation is sometimes seen with hydatidiform moles and chorionic carcinoma, but the ovaries return to normal when the primary tumour is removed. Unless hæmorrhage or torsion creates an emergency, operation is unnecessary. Edwards (1964) warned against doses which were too large, particularly in treating the Stein-Leventhal Syndrome. One patient in his series of 11 developed abdominal swelling due to grossly enlarged hæmorrhagic ovaries for which laparotomy was performed in another hospital. He advised hospital admission during treatment and carrying a note on discharge summarizing what had been done, and the suggested action to be taken should an emergency arise.

Clomiphene

Greenblatt (1961) discovered that a chemical compound MRL/41 (clomiphenecitrate) could induce ovulation in women. Related to chlorotrianisene, better known as Tace, clomiphene is an antiœstrogenic compound.* Bishop (1964) stated that of 5,000 patients treated with clomiphene in America 200 became pregnant. At Chelsea Hospital for Women 7 of 70 subfertile women conceived after taking the drug. Indications for treatment in 102 patients were primary amenorrhœa in 7, who received 100 mg. a day for 14 days; secondary amenorrhœa for which 200 mg. a day for 4 days was given, and metropathia hæmorrhagica. Excessive ovarian stimulation was a complication. Greenblatt (1961) advocated the continuous daily administration of 75 mg. to women with amenorrhœa until ovulation occurred, as indicated by a rise in basal temperature. Whitelaw (1963, 1964) found that prolonged or excessive doses produced gross ovarian enlargement, which sometimes caused acute abdominal emergencies requiring laparotomy as reported by

* Prepared by Wm. S. Merrell Company, Cincinnatti, Ohio.

Southam and Janovski (1962). He claimed 5 advantages for clomiphene over gonadotrophins as a means of inducing ovulation:

1. It is administered orally.
2. It is easier to obtain.
3. It is less liable to over-stimulate ovaries and produce polycystic changes.
4. Multiple pregnancy is less likely to occur.
5. Spontaneous ovulation is more likely to persist after stopping treatment.

Some of these views will probably be modified after further experience, for spontaneous ovulation following treatment is the exception rather than the rule, except in patients with dysfunctional bleeding. Clomiphene can possibly make the safe period safer by regulating the time of ovulation.

Toxicity

Hot flushes occur in over 30% of patients but disturbances such as nervousness, headache, diplopia, nausea, weight gain and frequency of micturition are present in less than 5%. Whitelaw *et al.* (1964) found no liver damage with tests including serum glutamic oxalacetic transaminase, alkaline phosphatase, and bromsulphthalein estimations. He advised that the dose should not exceed 750 mg. over a 5-day period and smaller doses proved effective in dysfunctional bleeding when œstrogenic activity was normal or excessive. Good results followed 150 mg. daily for 2 days followed by 100 mg. daily for 2 days.

Mode of Action

Whitelaw (1964), Smith and Kistner (1963) and Charles *et al.* (1963) agree that clomiphene acts primarily on the gonad, probably through enzymes. Its effect differs in the male and female, for large doses are associated with an increased excretion of pituitary gonadotrophins in a normal male, whereas this does not occur in normal menstruating women, nor has it always been demonstrated prior to induced ovulation as reported by Roy *et al.* (1963). This supports the view of Harris that the male and female brain are fundamentally different.

The administration of 200 mg. a day for 14 days to a male with hypophysial infantilism produced an 80% increase of 17-ketosteroid excretion and considerable improvement in subjective response. A similar increase in libido occurred in 2 other males with infantilism

reported by Whitelaw who referred to a report by Payne of a woman with Sheehan's syndrome who responded to clomiphene during the first course of treatment and conceived the following month.

The drug is anti-œstrogenic and in inducing ovulation is influenced by ovarian œstrogenic activity. The failure rate is high with an atrophic endometrium, whereas success is usual when it is adequately or excessively stimulated by œstrogens. Eighteen apparently normal women who failed to conceive over a minimal period of 1 year were given clomiphene 25–75 mg. daily for 2 days starting on the 5th, 6th or 7th day of the cycle and 3 became pregnant during the first month, but no other conceptions occurred in 6 months. Unlike the precision with which ovulation occurred in the HPG-HCG sequence there was no definite time relationship between the administration of clomiphene and the time of ovulation. In 60% of patients it was approximately 14 days after treatment, but the range was 2–41 days and the response varied even in the same individual. Ovarian enlargement was usual by the 4th day and Mittelschmerz was noted by 50% of patients who ovulated. Sixteen per cent of pregnancies were multiple.

Stein-Leventhal Syndrome

The results reported by Whitelaw (1964) in this group of patients are remarkable. He refers to a personal communication from Hoekenga claiming that of nearly 300 women with the Stein-Leventhal syndrome 82% ovulated. Whitelaw reported 8 patients, of whom 7 were married, treated by a bilateral ovarian wedge resection. Seven failed to respond and the 8th conceived, but amenorrhœa recurred after delivery. All 8 ovulated after clomiphene and 6 of the 7 married women conceived. Whitelaw agrees with Jeffcoate (1964) that conservative methods are indicated in the initial treatment of this syndrome. The success of clomiphene disproves the concept of a sclerosed capsule preventing ovulation. The fact that this preparation is not yet generally available serves as a warning that there are dangers associated with its use. Prolonged or excessive administration can involve the patient in disaster and the doctor in litigation in which he would have little defence (Chapter 9).

In welcoming this recent advance in therapy it is important not to forget the role which established procedures have filled. Stein (1959) reviewed 96 patients treated by wedge resection, the largest published series. Seventy-one were infertile and 63 (89%) conceived.

With a total of 146 pregnancies, they gave birth to 119 live babies, including 4 sets of twins. Only 3 failed to menstruate regularly after operation. By 1962 the same author had operated on 103 patients in none of whom amenorrhœa recurred. There were 76 infertile women and 67 (88%) conceived, producing 136 live infants, including 5 sets of twins. Stein (1963) believes that unsatisfactory results are due to faulty diagnosis and inadequate surgical techniques, and emphasized the role of gynæcography in precise diagnosis.

Summary

Clomiphene is an effective oral agent for inducing ovulation but ovarian overstimulation is a danger.

Population Control

In American and French literature a billion means a thousand million, whereas in English it is a million million, a difference which is important when studying population estimates, as when Rock (1964) estimated that "In 1975 the fourth billion will be on hand." In 1960 the world population was estimated at three thousand million. It had doubled since 1860, and at the present rate of increase will double again by the year 2000 to reach six thousand million. The problems of overpopulation and inadequate food emphasize the urgent need for drastic thinking and productive research. A recent advance has been the increasing world attention given to these matters and the willingness to review long established, sometimes deeply cherished, views and dogma. The Society of Friends recognized in 1949 the contribution which reliable contraceptive methods could make to marriage, and in 1958 the Anglican Lambeth Conference defining the distinction between intention and technique stated:

The Conference believes that the responsibility for deciding upon the number and frequency of children has been laid by God upon the conscience of parents everywhere, that this planning in such ways as are mutually acceptable to husband and wife in Christian conscience is a right and important factor in Christian family life and should be the result of positive choice before God.

The Methodists declared in 1961 that there was no moral distinction between contraceptive techniques, provided the means were harmless and acceptable to both husband and wife. Meanwhile the only method acceptable to the Roman Catholic Church is the so-called "safe period" with all its disadvantages. Twenty-five per cent of women are unable to use it effectively because of irregular

cycles and for the many who can there are other sources of error. In his Oliver Bird Lecture, "Sex, Science and Survival", Rock (1964) stated: "Five days of continence would preclude conception if only the couple knew which were the five days. We have not the time to wait for this knowledge." Powerful influences within the Church, including doctors, scientists and cardinals, are urging the need for a new look at these vital problems. The ruling that the Church condemned "deliberate intention and positive action taken by any means to deprive sexual union of its procreative potentiality" was reiterated in 1958 by Pope Pius, but willingness to review the problem is apparent in the action of Pope Paul in setting up a study commission to consider birth control. The health and happiness of millions, and possibly the safety of mankind, may well depend on the decision from the Vatican.

Meanwhile, the Family Planning Association of Great Britain, with Lord Brain as its President, has expanded rapidly. It has appointed Sir Theodore Fox, former editor of the *Lancet*, as its first medical director and, conscious of world needs, it launched a campaign in aid of international family planning in 1963. To help countries anxious to employ new techniques the Association is expanding training facilities for overseas students. There are already over 8,500 family planning clinics in India, with a comparable number in Pakistan, where the Governments are taking an active part in an intensive drive to reduce the birth rate. Both male and female sterilization are encouraged and a small inducement is offered to the male who submits to vasectomy. In Britain the number of clinics is increasing and in 1963 the number of new patients was 335,037, a rise of 12% on the previous year. In 1963, 282 clinics prescribed oral contraceptives as opposed to 163 in the previous year, and the number of patients using this method rose from 3,536 in 1962 to 13,670 in 1963.

Unless motives are right, clinics and contraceptive techniques are unlikely to make their fullest impact. Men and women who are indifferent to the welfare of their children are unlikely to be impressed by reference to the responsibilities of procreation. In all communities some of those most in need are the ones who fail to use the services offered. Religious and political factors are also important and in some developing countries the ignorant and dishonest make political capital of family planning by representing it as an attempt to eliminate the black man. It is tragic that this happens where help is required most urgently as shown by Williams (1964) (Table 41).

Table 41

MORTALITY RATES (1961)

(Williams)

Country Status	Death Rate	Birth Rate	Infant Mortality Rate	
ADVANCED	10	16	20	
Average life span ▷	▬▬▬▬▬▬▬▬▬▬▬▬▬▬▬ ▷			70 yrs.
INTERMEDIATE	14	30	70	
Average life span ▷	▬▬▬▬▬▬▬▬▬ ▷ 50 yrs.			
PRIMITIVE	20	50	200	
Average life span ▷	▬▬▬▬▬ ▷ 35 yrs.			

Death Rate = deaths per year per 1000 living persons.
Birth Rate = births per year per 1000 living persons.

Infant mortality = deaths in babies under 1 year per 1000 live births.

Contributions of major importance are the pill and plastic intra-uterine devices (I.U.D.), an abbreviation with a sinister significance for most obstetricians! According to the Population Investigation Committee of the London School of Economics most married couples rely on the sheath and coitus interruptus and only 1 in 7 seek professional advice. A similar American survey revealed that the sheath is used by 43%, although the woman is more dominant than the British wife in selecting an acceptable method. Religious belief exercised an important influence and two-thirds of the Roman Catholics interviewed relied on the safe period. It is not recorded how many found it dangerous.

The Pill

In 1955 Pincus reported in Tokyo on some effects upon reproduction of progesterone and related compounds. New synthetic preparations, including the 19-norsteroids, were tested first on animals and then on women and one of them, norethynodrel (Enovid), was used in the first contraceptive field trial in Puerto Rico in 1956. Cyclical administration from day 5 to 25 was used to

achieve two things, the inhibition of ovulation and the maintenance of menstrual rhythm. A combination of an orally active 19-nor-progestational steroid with a small dose of œstrogen was most effective in doing this. Initially, 10 mg. of norethynodrel plus 0·15 mg. of ethinylœstradiol-3-methyl ether was used, but the dose was reduced to 5 mg. norethynodrel with 0·075 mestranol (Conavid) and ultimately to 2·5 mg. norethynodrel plus 0·1 mg. mestranol (Conavid E). Pullen (1962) found this effective as a contraceptive but associated with a 30% incidence of menstrual irregularity with spotting and breakthrough bleeding which was controlled by increasing the dose to $1\frac{1}{2}$ tablets. A similar preparation consists of 5 mg. lynestrenol with 0·15 mg. mestranol (Lyndiol). This group is the most œstrogenic of all oral contraceptives because the pro-gestogen is metabolized into œstrogen in addition to the œstrogen each tablet contains. The clinical implications of this are discussed later.

The Food and Drug Administration of the United States approved norethynodrel as an oral contraceptive in 1960. A second group of progestogens was later developed. The first to be approved consisted of 2 mg. of norethisterone with 0·1 mg. mestranol (Ortho Novin). Other potent preparations are: 4 mg. norethisterone acetate with 0·05 mg. ethinylœstradiol (Anovlar); 2·5 mg. norethisterone acetate with 0·5 mg. ethinylœstradiol (Norlestrin); and 1 mg. ethynodiol diacetate with 0·1 mg. mestranol (Ovulen). Norethisterone acetate 3 mg. with 0·05 mg. ethinylœstradiol (Gynovlar) was the first oral contraceptive in Britain to be submitted to the Dunlop Committee for the investigation of new drugs and permission was given for its use in March 1964. It resembles Anovlar except that it contains 3 mg. instead of 4 mg. of progestogen and is supplied in a 21-tablet pack to be used for 3 weeks, commencing on the 5th day of men-struation.

Meanwhile, a third group of compounds was synthesized from 17-hydroxyprogesterone. They are not metabolized to œstrogen and have a powerful progestational effect on laboratory animals, though this is less marked in women. The only one at present available commercially is Volidan, which, like Anovlar and Norlestrin, reduces the menstrual loss in approximately 70% of patients. It consists of megestrol acetate 4 mg. with ethinylœstradiol 0·05 mg.

World-wide experience has proved beyond doubt that these drugs are the most effective contraceptive agents at present available. Jackson (1963) stated that at least one and a half million women in the United States were using oral contraceptives and Winter (1965)

stated that the number of women using Enovid in the United States in 1963 was 2,280,000. There was a four-fold increase from 1962–63 in the use of oral preparations at family planning clinics in Britain.

Mode of Action

Experimental work showed that oral progestogens suspend the excretion of gonadotrophin. Mating induces ovulation in the mature rabbit, but not if an oral progestogen is given first, although if gonadotrophic hormone is administered the animal ovulates, confirming that ovarian response is unaltered. In hypophysectomized or immature rats treated with norethynodrel the ovaries respond if gonadotrophins are given (Eckstein and Mandl, 1962). The gonadotrophin content of the pituitary glands of rats and mice treated by oral contraceptives has been measured. Weight changes of ovaries and uteri were recorded after injecting homogenized pituitary preparations into immature female rats. Saunders and Drill (1958) demonstrated that norethynodrel depressed gonadotrophin production but Hecht-Lucari (1964) found that it was greater after the administration of octyl-ether-norethisterone and concluded that the steroid interfered with the release but not the production of the hormone.

Nelson and Patanelli (1960) suggested that luteinizing hormone might be inhibited by smaller amounts of steroid than were necessary to suppress follicle-stimulating hormone. Spermatogenesis is controlled by follicle-stimulating hormone and they found that double the amount of norethynodrel and norethisterone was required to suppress spermatogenesis than to inhibit the secretion of androgens. Hecht-Lucari (1964) showed that corporea lutea were smaller, and luteinization less intense, in rats treated with gonadotrophin and norethisterone than in those given gonadotrophin alone.

Gonadotrophin levels in postmenopausal women are normally high and Rosemberg and Engel (1960), and others have studied the effect of the new steroids on these. Douglas *et al.* (1960) and Martin and Cuningham (1960) investigated the urine of postmenopausal women with breast carcinoma and found that norethisterone preparations reduced the gonadotrophin excretion, but even large doses merely brought it down to levels normally found in healthy premenopausal women. They concluded that norethisterone was weaker than stilbœstrol as an inhibiter of pituitary gonadotrophin secretion. Bucholz *et al.* (1964) demonstrated changes in luteinizing hormone secretion similar to those in the total gonadotrophin, but confirmed that the new steroids do not abolish it in postmenopausal women.

Similar findings were reported in the male by Apostolakis (1961) and Heller *et al.* (1960).

Brown, Fotherby and Loraine (1962) described a different pattern of behaviour in premenopausal women. After 10 mg. daily of norethisterone from day 5 to 25 there was no decrease in gonadotrophin excretion although ovulation was inhibited. This was confirmed by Matsumoto Ito and Inoue (1960) but Garcia and Rock (1960) found that both Enovid and norethisterone reduced the gonadotrophin level. An explanation of these apparently opposing views was offered by Bucholz, who demonstrated that the peak of gonadotrophin excretion in a normal ovulatory cycle was abolished when ovulation was inhibited, but the basal level was maintained. The œstrogen in the compounds probably impairs gonadotrophin secretion and inhibits ovulation, but the progestogen effect on pituitary function is not yet known. An important point is the rapidity with which normal function is restored when the progestogens are discontinued and animal experiments suggest that the end products of norethynodrel and norethisterone metabolism are excreted within a week in urine and fæces. Little is known about the metabolism of oral contraceptives in women, but the rapid response of withdrawal bleeding suggests that absorption and excretion are rapid. The time interval between the end of treatment and the beginning of bleeding varies with different compounds and on the 20-day cycle of administration menstruation usually returns on the 28th day with Lyndiol, the 26th day with Norlestrin, and varies between the 26th–27th days with other preparations. With the 21-day administration of Gynovlar the cycle is usually 28 days.

Holmes and Mandl (1962) stated that it is not known whether the orally active 19-norsteroids cause temporary sterility by their effect on the pituitary, the ovary, or the reproductive tract, nor is it possible to say that œstrogens and orally active progestogens act on the human pituitary as they do in rats and mice in which prolonged œstrogenic stimulation has been followed by tumour formation. No such case has been reported in women, although thousands have used the pill for 7–9 years and many others have taken much larger doses of the same preparations as treatment for endometriosis. The oral contraceptives produce progestational changes in endometrium, vaginal epithelium, and cervical mucus. These impair penetrability of the mucus by spermatozoa and even if ovulation occurred implantation would be highly improbable because of the state of the endometrium. It appears, therefore, that there is at least this triple bar to conception.

The observation of Garcia, Pincus and Rock (1958) and Pincus *et al.* (1958) that infertility ceased when the pill was discontinued was received with caution, but subsequent evidence supports this view. In fact, fertility appears to be increased temporarily and Goldzieher *et al.* (1962*a*) found a pregnancy rate of 66 % in the post-treatment cycle compared with 35 % when mechanical contraceptives were discarded. The rate was 90 % within the first 3 months. Mears (1965) reported that 80 % of 104 patients conceived within 2 months of discontinuing the pill in London trials. For this reason it is sometimes given for 2–3 months to "normal" infertile couples in whom no explanation has been found for sterility. Conception should occur within 3 months of stopping treatment.

Safety

Two aspects must be considered, safety as a contraceptive, and safety in terms of possible serious repercussions.

Contraceptive Safety

The pill is so efficient that if doctors believe what some patients claim it is even safer than total abstinence! Rice-Wray *et al.* (1962) reporting on the prolonged administration of norethindrone stated that no patient who followed the instructions conceived, but 3 pregnancies occurred after failure to take the tablets on the 8th and 9th day of one cycle, days 10 and 11 of another, and after the 19th day in a third. Goldzieher (1962) had no unplanned pregnancy in 6,139 cycles involving 210 women. *The pill is the most effective of all contraceptive agents and provides complete control with one reservation.* During the first month the patient should employ an additional method because a few pregnancies have occurred in the first days of its administration, particularly with a cycle of less than 26 days.

Patient Safety

Animal research into the prolonged effect of œstrogens made some anxiety inevitable concerning possible carcinogenic effects, although the œstrogen content of these compounds is small. Using larger doses than those now recommended, none of the 913 women under observation for periods of 6–9 years in the Puerto Rico trials developed carcinoma of any reproductive organs. Moreover, 70 % with suspicious smears at the start of the trial had negative tests within a year. More recently, however, Attwood (1965) reported

dyskaryotic changes associated with use of the pill at Birmingham and stressed the need for careful supervision and repeated smears. Further studies are in progress.

The effect of the tablet is progestational rather than œstrogenic, and the administration is cyclical. Moreover, exogenous œstrogens cause a decrease in endogenous hormone secretion and it is the latter which may possibly be carcinogenic. There is evidence to incriminate prolonged endogenous œstrogenic stimulation with endometrial hyperplasia in the ætiology of corpus carcinoma, but the endometrium in patients taking the pill is never hyperplastic. Thousands of endometrial biopsies have been performed on women taking the oral contraceptives. The endometrium varies according to the preparation used. Glands are more plentiful with larger nuclei under the influence of norethynodrel than when norethisterone is used, either alone or in combination with an œstrogen as in Anovlar, which in both cases produces a picture of static hypoplasia. Small scattered glands are separated by a relative excess of dense stroma showing pseudodecidual changes at the end of a 20-day cycle (Jackson 1963). The possible long term effect of these regressive changes would be a decreased risk of endometrial carcinoma for women using the progestogens for long periods either as a contraceptive or therapeutically to control dysfunctional uterine bleeding.

A *Lancet* (1962) editorial emphasized the importance of the long term view but admitted that where other methods were impossible or ineffective the undoubted reliability of oral contraception had to be weighed against theoretical long-term risks. To speak of methods proving ineffective implies that unplanned pregnancy has occurred and this is a hazard which must be accepted by every method of contraception other than the pill. If for any reason it is considered inadvisable to accept this risk the pill or abstinence are the only alternatives apart from sterilization.

Acceptability

An essential requirement for contraceptive efficiency is that the method must be acceptable to the patient. The more this is so the less the likelihood of her defaulting. In the Puerto Rico trial there was a failure rate per 100 woman years of only 1·7 in a low income group. The risk increases with every missed tablet and should a patient forget it one night she is wise to take two the next. Mears (1964) found that 4% of cycles were associated with missed

tablets in spite of which there were only 12 pregnancies among 2,000 patients in 20,000 cycles. Among problem families the acceptability rate is higher than with other preparations and the failure rate lower. Increasing numbers of women are asking for the pill. At the New York University—Bellevue Medical Center in 1962 90% of new patients chose oral contraception in preference to vaginal methods. The increase from 3,535 in 1962 to 13,670 in 1963 at family planning clinics in Britain is further evidence of acceptability. A study was made by Frank and Tietze (1965) of 14,000 patients to whom Enovid had been given as an oral contraceptive. Two and a half years later 75% were still using the preparation.

Side Effects

In the early trials Pincus found 27% of patients discontinued using the pill because of unpleasant complications, while Cook, Gamble and Satterthwaite (1961) had the same experience with 22% using norethindrone. Pincus considers side effects are largely iatrogenic and vary in proportion to the warnings doctors give concerning them. The less said the fewer complaints. Social status appears to be a factor, with more side effects among private patients. Newer preparations with smaller doses of hormone are more acceptable, and withdrawal from trials fell by one-third when the dose of norethynodrel was reduced from 10 to 5 mg., but the following complications still occur, although to a decreasing extent.

1. Nausea.
2. Breast discomfort.
3. Breakthrough bleeding.
4. Headaches, dizziness, abdominal cramps.
5. Weight gain and increased appetite.
6. Diminished flow.
7. Amenorrhœa.
8. Acne.

Satterthwaite (1964) made a comparative study of low dosage oral contraceptives. The choice of tablet for a particular patient is important. For example, if a woman has breast discomfort before taking the pill it is wiser to prescribe Conovid or Lyndiol because of their relatively small progestogenic effect. The œstrogenic action of these is an advantage when there is acne or hirsutism. Menorrhagia requires a progestogenic tablet such as Anovlar, Norlutin, Ortho Novin or Ovulen. Conversely, if oligomenorrhœa causes anxiety it is

better to use a preparation with more œstrogenic action such as Conovid or Lyndiol. Breakthrough bleeding is less common with Anovlar and Lyndiol, and when it occurs the dose should be doubled for 3 days or another preparation used. If amenorrhœa develops the patient can be assured that she is not pregnant providing she has taken the tablets as advised, but if changing to the 17-hydroxyprogesterone Volidan does not restore normal rhythm it is wise to stop the pill and use another technique until menstruation returns. A different preparation can then be tried.

Mears (1962) found only 7 of 166 highly fertile women who disliked conventional contraceptive techniques withdrew from a clinical trial of Anovlar because of side effects, the most common of which was weight gain. Breakthrough bleeding occurred in 5% and decreased menstrual flow in over 60%. Premenstrual tension was relieved in 26%. Nausea is usually temporary, can be reduced and sometimes prevented by taking the tablet with the evening meal and if this fails by changing to a less œstrogenic preparation such as Anovlar or Norlestrin. It is better to change from one preparation to another at the beginning of a cycle. Many patients have no side effects and say they have never felt better than when taking the pill.

Lactation

Inhibition of lactation would make it unacceptable to many women, particularly in Eastern countries, but no adverse effect was reported in the Puerto Rico study. In the Mexican series Rice-Wray believed there was some degree of suppression in approximately one-third of lactating mothers.

Libido

When a preparation proves acceptable libido, if affected at all, is usually improved, which is not surprising in view of freedom from the fear of pregnancy, but some women have decreased desire. The reason for this is not understood.

Thrombo-Embolism

In the United States in 1961 two healthy young women died from embolism while taking Enovid, thus raising the possible ætiological relationship between 19-norsteroids and thrombosis. Six fatal and 100 non-fatal cases in American women taking Enovid, together with one in England and one in Norway were reported. A sub-committee

of the Food and Drug Administration investigated the problem and concluded that there was no significant increase in the risk of thrombo-embolic disease with the use of oral contraceptives. Seven patients out of a total of 2,000 developed thrombosis during the London trials of new preparations, but this was considered to fall within the normal range. Morrell *et al.* (1964) assessed the incidence of spontaneous thrombosis in non-pregnant females of childbearing age as 1–3 per 1,000. It possibly occurs more frequently during pregnancy but accurate figures are not available, although fatal embolism occurs once in approximately 20,000 pregnancies and confinements (Chapter 1). Thrombophlebitis has not been reported with large doses of Enovid in the treatment of endometriosis. Some patients continued using the contraceptive pill when thrombosis occurred and the condition cleared. In others phlebitis developed after the drug was stopped. Hæmatological studies have not revealed any factors which could initiate clotting, and no causal relationship has been demonstrated between the administration of these compounds and the incidence of thrombosis, but until the problem has been investigated further many would prefer not to prescribe oral contraception for women with a history of phlebitis. There are others with considerable experience of oral contraception who consider this to be an unnecessary precaution. In the study reported by Frank and Tietze (1965) only 7 patients in 14,157 developed thrombophlebitis while taking Enovid. There were no embolisms and no deaths. This incidence was lower than the expected rate in a similar group of women not taking the oral contraceptive. On the other hand the latest figures available in Britain to the Family Planning Association in January 1966 recorded 16 deaths from thrombo-embolic lesions in an estimated 400,000 women using oral contraception. Eight of these died from pulmonary embolism and 5 from coronary occlusion. The estimated number of deaths due to thrombo-embolic episodes in 400,000 women between the ages of 15 and 45 not taking oral contraceptives would be 13. There is thus no significant difference between the actual number of deaths and the estimated number although the actual number of fatal pulmonary emboli is greater than would be expected, whereas the deaths from coronary occlusion are fewer. More evidence is required before a final assessment can be made on this difficult problem. It is obvious that there should be accurate records of the mode of death of every woman who dies from thrombosis or embolism between the ages of 15 and 45. Death from a thrombo-embolic lesion may be apparently spontaneous, follow surgical trauma, or complicate a disease such as typhoid or pneu-

monia whether the patient was taking oral contraceptives or not. All factors of possible significance must be recorded if false conclusions are to be avoided in statistical analysis.

Liver Damage

Eisalo *et al.* (1964) reported hepatic impairment as measured by elevated serum transaminase levels and bromsulphthalein retention in 7 postmenopausal women treated for 28 days with Lyndiol. The investigation was carried out because of structural similarity between oral contraceptive steroids and oral anabolic steroids, the use of which was shown by Drill (1963) to be associated with risks of hepatic dysfunction and jaundice. Eisalo demonstrated in one patient hepatic changes similar to those associated with the administration of Lyndiol when only the œstrogen component was given. The progestogen factor had no effect. He postulated that the uniform results obtained in the 7 postmenopausal patients could be due to a synergistic action between the two components. Further research is indicated, together with an accurate clinical record of side effects, including those possibly due to hepatic dysfunction. All family planning clinics keep records of patients using the pill and the Dunlop Committee, with functions similar to those of the Food and Drug Administration in America, has emphasized the importance of doctors notifying any unusual side effects during use of these drugs. With the number of women using oral contraception some will inevitably develop jaundice from intercurrent disease, and there have been women with hepatitis who continued taking the pill and the jaundice subsided in the usual way.

Sequential Regime

The rationale of this routine is to inhibit ovulation with œstrogenic hormone during the first half of the cycle and to maintain a normal type of endometrium with progestogen in the second half. A disadvantage in terms of acceptability is that two tablets are not as simple as one. Moreover, in some reports there has been a greater incidence of failure with this routine, although evidence varies in different countries. The failure rate was highest in Britain and New Zealand and lowest in Mexico, where Rice-Wray recorded no pregnancies due to tablet failure in 13,000 cycles on sequential therapy (Mears 1965).

Occasional breakthrough ovulation occurs with oral contraception without pregnancy following. This could be explained by the effect

of the pill on the endometrium and cervical mucus. The former is unsuitable for implantation of the fertilized ovum and the latter hostile to sperm penetration. If ovulation occurred during sequential therapy neither of these safeguarding factors would operate and the risk of pregnancy should be increased. At present there seems little in favour of this method of treatment apart from the probably academic advantage of mimicking the normal cyclical changes in the endometrium.

While it is true that certain long-term effects of oral contraception cannot yet be accurately predicted it is reassuring to note that as experience accumulates anxieties are eased. Possible, though improbable, delayed dangers must be weighed against the risks of pregnancy and abortion and when there are medical contra-indications to conception the choice is easy.

Intra-uterine Devices

These include rings, spirals, loops and bows. The metal ring introduced by Gräfenberg over 35 years ago became popular in some European countries but was viewed with such disfavour in Britain, the Commonwealth, and America that it was either not mentioned or was associated with the sinister armoury of an abortionist. In spite of opposition it was used sufficiently often for such complications as pelvic sepsis, irregular bleeding, perforation of the uterus, and pregnancy to be well recognized. To what extent these were due to dangers inherent in the ring or to carelessness in its use was not established. Some gynæcologists, of whom the author (J. S.) was one, used it as an alternative to tubal ligation in young women when other contraceptive measures failed and pregnancy was contra-indicated for medical reasons. Experience proved it to be acceptable and effective, a view shared by Dr. Margaret Jackson of Exeter (personal communication) who started using rings in 1939 for the "fertile and feckless".

They should be inserted in the postmenstrual phase with aseptic technique and preferably without anæsthesia. Disturbing an early pregnancy is thus avoided and the risk of infection is reduced. Confirming the axis of the uterine cavity with a sound before inserting an intra-uterine device reduces the danger of perforation. Animal experiments suggest that the appliance stimulates utero-tubal peristalsis so that the ovum reaches the uterine cavity before the endometrium is prepared for implantation. The failure rate is approximately 1%. A disadvantage of the Gräfenberg ring is that

it can bury itself in the myometrium or be extruded into the Pouch of Douglas or broad ligament when left in position for long periods. For this reason it should be changed annually. It is also easy to perforate a recently pregnant uterus, particularly when the ring is inserted under anæsthesia.

The first plastic device for human use was a Japanese ring with a 2 cm. diameter. Three American-designed polythene intra-uterine devices (I.U.D.'s) are the Margulies spiral, Lippes loop and Birnberg bow. It is claimed that they cause no reaction, are pliable, easily inserted and removed, can be introduced without preliminary cervical dilatation, and can be left in place indefinitely. An incorporated barium salt makes them radio-opaque. A fourth device, the Hall-Stone stainless steel ring, has been in use for 15 years.

Large scale clinical trials of these appliances are in progress in America, Britain, Israel, Japan and elsewhere, and more should soon be known of their relative merits. It appears that the Margulies spiral and Lippes loop have the lowest failure rate, approximately 1%. Most patients have spotting or increased menstrual loss for the first cycle and sometimes for several months. If menorrhagia continues the device should be removed. Abdominal cramps due to uterine irritation occur in 10–25% of patients. The spiral and loop have the theoretical and possibly practical disadvantage of protruding from the cervix and offering a direct pathway to the uterine cavity for infection from the vagina. The Birnberg bow is free from this objection but at the time of writing the Lippes Loop in its two largest sizes, C. and D, is the device considered most satisfactory by the medical committee of the International Planned Parenthood Federation (I.P.P.F.). Those who wish to consider in more detail the effectiveness and acceptability of these devices are referred to a review of intrauterine contraception by Tietze and Lewit (1964). Publication No. 24 of the *National Committee on Maternal Health, New York*, is a reprint of this article. Guttmacher (1965) has reviewed a world-wide experience of the intrauterine devices.

Sterilization of Intra-uterine Devices

These cannot be autoclaved and should be stored in a solution of 1/1,000 Benzalkonium chloride for a minimum of 24 hours before use. No ill-effects on pregnancy or fœtus were recorded when pregnancy occurred with the device in position, as happened in 2·5–5% of patients during clinical trials. The appliance was removed in approximately 5% of patients because of menorrhagia or pain.

Efficiency of Contraceptives

The contraceptive efficiency of different techniques as assessed by the failure rate per hundred years of use, has been summarized as follows:

1. Oral contraceptives 0–1·7.
2. Intra-uterine devices 2·5–5·5.
3. The sheath 14.
4. Caps and chemicals 14.
5. Coitus interruptus 17.
6. The safe period 38.
7. Douches 40.

Common Failures of Fertility Investigation

Davidson (1961), stated that the investigation of a childless couple may fail for two main reasons, ignorance and inadequate correlation of available information. Ignorance and disregard of essential fertility factors are often associated, as when a husband is not examined. Investigations, whether thorough or incomplete, may not be followed by careful interpretation of the findings. An inaccurate assessment of the cause of infertility is then likely to be made, as when a postcoital test is not performed because of a good sperm count. The significance of a low seminal volume, scanty or infected mucus, a capacious vagina, and indifferent coital technique may thus be overlooked.

Many infertility problems are unsolved because of two widely held misconceptions:

1. That infertility is a clinical entity.
2. That arbitrary standards of normality can be used as absolute diagnostic guides.

Infertility is not a clinical entity, but a symptom complex with an almost infinite number of possible ætiological variations. Good medical practice demands accurate diagnosis before treatment is advised, but in no branch of medicine is this fundamental concept ignored more often than in the alleged treatment of infertility. Many a doctor who would not treat a patient with pain in the chest without discovering its origin prescribes hormones, diathermy, or

repeated insufflations for infertility before determining the reason for it. The patient may not even be infertile!

When a woman was reluctant to visit her doctor because she failed to conceive there were good reasons for assuming some degree of impaired fertility after years of barren marriage. The situation is now changed. An increasing number of patients from a better informed public request help early if pregnancy does not occur. This change in patient attitude introduces new problems. The earlier in marriage a woman complains of infertility the more likely it is that she is not infertile. Tietze, Guttmacher and Rubin (1950), and Barns and his colleagues (1953), have shown that from 80 % to 90 % conceive within a year of continued endeavour. Approximately 60 % are pregnant within 3 months and by the end of 6 months the figure is 70–80 %. The rationale of infertility investigation is the opportunity it offers of selecting from the total group that small minority with a demonstrable cause for their failure to conceive. It may or may not be amenable to treatment. The literature is confused by unsubstantiated claims for therapeutic success in patients in whom no lesion was confirmed. Empiricism is not a sound basis on which to build scientific advances.

A more serious aspect of this problem is that injudicious medical intervention may delay conception. Infertility can be iatrogenic and the emotional repercussions of misunderstood or ill-formed advice are often not appreciated. Disappointment produces tension, and tension impairs function in both male and female. Evidence is accumulating of the damaging effect of stress, a better understanding of which constitutes a major advance.

MacLeod (1963) correlated changes in human seminal cytology with illness, the administration of toxic substances, allergic reactions, and even with stress. Interference with spermatogenesis is reflected by a depressed sperm count, an altered ratio of types of spermatozoa and by the exfoliation of immature germinal cells. In a healthy male none of these changes should be found for their presence indicates a non-specific testicular reaction to trauma. MacLeod (1961*a*) initiated this research when investigating the effect of antispermatogenic compounds on healthy fertile males. He observed that many of the changes taking place resembled in detail the seminal picture "which appeared frequently enough in the thousands of individuals we have studied for infertility". These were oligospermia with a count of 1–2 million per ml., poor motility, poor morphology, as evidenced by a high percentage of tapering forms (20–90 %), and immature cells, particularly large spermatids, accounting for 10–90 %

of the total cellular content of the ejaculate. MacLeod suggested that the most probable explanation of these findings was an endogenous hormonal disturbance insufficient to produce any outward change in masculinity but powerful enough to affect sensitive germinal epithelium. Preliminary investigations suggested that steroid excretion was not normal in these males and the output of 17-ketosteroids and 17-ketogenic steroids was increased. Further research may provide an explanation of the stress syndrome influenceing testicular activity through the adrenal cortex. MacLeod (1963) stated:

It now seems possible that the environment of everyday living may play an important role in the ætiology of human male infertility, and that congenital factors may not be as important in the sense of a man being born with inherently good, poor, or indifferent testicular function.

The research is important in the development of a male contraceptive pill and Moench and Holt (1931) suggested that the cytology of the human ejaculate had a specific pattern peculiar to the individual analogous to the specificity of his fingerprints. Subsequent work by MacLeod (1962, 1963) supported this view. Studies were made of testicular response in volunteer prisoners during a severe allergic reaction to the mercurial antiseptic merthiolate, and to the administration of 6-medroxy-progesterone acetate (depot-provera). Comparative sperm morphology in three populations of 600 prisoners, 250 subfertile men, and 66 with varicoceles is given in Table 42. MacLeod suggested that the presence of more than 2% of immature cells was evidence of testicular stress, just as the presence of normoblasts in the blood could indicate abnormal marrow

Table 42

COMPARATIVE SPERM MORPHOLOGY IN THREE POPULATIONS.

(MacLeod, 1963)

Population	·········· mean % ··········			
	Oval	Small	Tapering	Immature
PRISONER (600)	76	9	4.0	0.3
PATIENT (250)	55	11	13.5	3.0
VARICOCOELE (66)	30	11	25.0	14.0
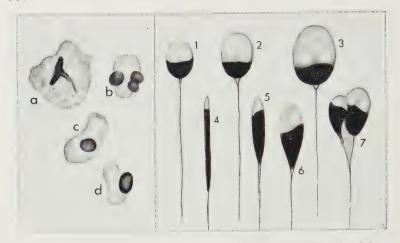
Fig. 51. 2 represents the normal oval healthy spermatozoa. 1 and 3 are smaller and larger versions of the oval cell, whereas 4–7 reveal tapering and abnormal forms.
Immature forms are illustrated in a, b, c, and d. They include spermatids with eccentric and peripheral nuclei and multinucleated cells.

stimulation. The main types of mature and immature cells are illustrated in Fig. 51. From human and mammalian studies he deduced that spermatozoa liberated from germinal epithelium at any given moment are not ejaculated until at least 2 weeks later as their passage through the epididymis takes approximately 14 days. If impaired motility is seen within 14 days of exposure to a toxic influence it must be assumed that this has acted directly on mature cells already in the ducts, quite apart from any action on the germinal epthelium which would be revealed later by the appearance of immature forms. The normal mature sperm is oval, and in a good seminal specimen 76% or more will be of this shape and constant in size. Others will be smaller or larger. The pattern characteristic for each individual will return when health is restored after illness. The mean percentage incidence of oval spermatozoa is reduced in infertile men, and in males with varicoceles. Even more important is the rise in percentage of tapering forms of mature spermatozoa and of immature forms, both of which according to MacLeod are an indication of trauma, be it infection, excessive warmth, toxic drugs, or emotional stress. In his opinion *the exfoliation of immature cells is the most important of these features in diagnosis and prognosis.* The

incidence of these was increased tenfold in subfertile men, and nearly 50 times when subfertility was associated with varicoceles (Table 42).

Suppression of Spermatogenesis

The pattern of both testicular suppression and regeneration was revealed when MacLeod (1961b) investigated the cellular content of ejaculate during the administration of an amœbicide, a bis-diamine compound which was found to be highly antispermatogenic. When 500–1,000 mg. were given twice daily the sperm count was severely depressed in about 60 days and reached zero at 80–100 days. There was profound impairment of motility and an increase in abnormal forms with a rising incidence of immature cells which sometimes appeared as the first evidence of impaired function, before either count or motility were affected. The first immature forms to appear are spermatids with eccentric and peripheral nuclei which may be extruded. Subsequently bizarre often multinucleate forms appear (Fig. 51). Similar changes followed the injection of 6-medroxy-progesterone acetate, 100 mg. weekly or a single intramuscular injection of 1,000 mg. Marked depression of count and motility with the appearance of small amorphous forms was apparent within 45 days. By the 59th day tapering mature spermatozoa and immature cells were seen, and the sperm count reached zero between days 59–108. Signs of regeneration appearing 147 days after the injection were small tapering motile spermatozoa. A sperm count was possible by the 164th day but the normal pattern was not restored for 300 days. Absence of feminizing signs or loss of libido was an important feature of this potent antispermatogenic hormone. MacLeod considered that the effect was produced by depressing the secretion of pituitary follicle-stimulating hormone, unlike the action of dichloro-acetyl diamines on the testes and not at pituitary level (Heller et al., 1961).

Summary

The seminal cellular content in a healthy male is characteristic of that individual, and tapering forms and immature cells are a manifestation of stress. An effective male contraceptive acting by completely suppressing spermatogenesis is a possibility. The ejaculate cytology represents testicular activity of at least 14 days previously because the passage of spermatozoa through the epididymis takes approximately 14 days.

Varicocele

In 1952 Tulloch of Edinburgh ligated spermatic vessels in the treatment of bilateral large varicoceles on a sterile man. His fertility was restored. Three years later Tulloch (1955) reported the results of operating on 30 infertile men with varicocele. The sperm count was unaltered in 10, but greatly improved in 20, including two men with azoospermia whose wives conceived. Scott (1960, 1961) had similar success in a series of 55 varicocele operations after which 35 men had counts of over 20 million spermatozoa per ml. with at least 50% actively motile 4 hours after ejaculation. Young (1961) described a series of 97 consecutive cases, including 16 men with azoospermia in 3 of whom spermatogenesis was restored. Post-operative studies were performed on 72 of the remainder and 48 had an improved count with increased motility. He accepted Scott's classification of varicoceles into large moderate and small, and agreed that the frequency and extent of subfertility was proportional to the size of the varicocele. In Scott's series only large varicoceles had a significant effect on sperm count, but the motility was influenced to varying degrees by all sizes.

Mode of Action of Varicocele

Human testicular temperature, like that in many mammals, is normally maintained below body temperature. In undescended or ectopic testes spermatogenesis does not occur. Normal function requires a temperature 2°C cooler than body temperature, and any decrease in temperature gradient impairs spermatogenesis, but when a testis kept at body temperature is cooled spermatogenesis may occur. Varicoceles can increase intrascrotal temperatures by almost 3°C, and although they are usually unilateral and left sided the raised temperature can be detected in both testes. Similarly, even small hydroceles depress testicular function by raising the temperature. The larger the varicocele or hydrocele the greater the chance of subfertility. Scott (1961) reported operative results in 109 varicoceles of large or moderate size and 66% of patients with a count of 6–20 million before operation were fertile within 6 months, while others with azoospermia and exceptionally low counts also responded. Sperm count and motility continued to improve for 2 years, at which time counts were sometimes 5 times better than they were 6 months after operation. All these patients were partners to wives sterile for periods of 2–10 years, but 30% of these conceived within a few months of operation on the husband.

Summary

Varicoceles and hydroceles depress spermatogenesis by increasing scrotal temperatures. The larger they are the higher the temperature, and the greater the degree of subfertility. They are a serious cause of infertility and adequate treatment is followed by progressive improvement of spermatogenesis in 60–80%, with an appreciable conception rate.

Cryptorchidism

The effect of this on fertility is due to the raised temperature of the gonad. Wangensteen (1927) showed that in dogs germinal epithelium depressed by artificial cryptorchidism can regenerate provided the testis is returned to the scrotum before complete degeneration occurs. Scott (1962) proved that the same applies in man, and correctly timed treatment improves fertility. Untreated bilateral cryptorchidism inevitably causes total sterility, and even when unilateral there is a high incidence of impaired fertility which Scott (1963) showed could be halved by correct treatment. Fertility can be preserved in an appreciable percentage of men with bilateral lesions if treated before puberty. Assessment is made on three points:

1. The type of cryptorchidism.
2. The form of treatment to be employed.
3. The age at which it should be used.

Scott emphasized the importance of recognizing three types of cryptorchidism and choosing the appropriate treatment. They are:

1. *Retractile or Migratory Testes*

These are normal gonads elevated by powerful cremaster muscles and occupying the superficial inguinal pouch, which is an extension of the scrotal compartment. With patience the testis can be manipulated into the scrotum (Denis Browne, 1933). Retractile testes function normally and require no treatment.

2. *Ectopic Testes*

These are prevented from entering the scrotum by a fascial barrier which diverts the testis into the groin superficial to the external oblique aponeurosis. Division of the barrier and placing the gland in the scrotum is the logical treatment.

3. *Undescended or Retained Testes*

These have failed to pass through the inguinal canal and are often atrophic and associated with congenital abnormalities of the epididymis as reported by Badenoch (1946).

Mack *et al.* (1961) demonstrated widespread degeneration of germinal epithelium in the undescended testis, and this, together with the high incidence of congenital malformations, makes the prognosis poor. Charny and Wolgin (1956) showed that if spontaneous descent occurred up to the 10th year spermatogenesis was not adversely affected, but after this there is a high incidence of tubular degeneration even if the testis descends into the scrotum. Scott (1962) advised treatment with gonadotrophins between the 8th and 10th year, followed by orchidopexy if descent does not occur within 3 months.

Tight fitting scrotal supports and warm underpants influence spermatogenesis adversely. Davidson (1961) described an infertile male with a sperm count of 6–11 million per ml. with poor motility and morphology. He wore a scrotal support for a small left varicocele, and was advised to abandon the support and to bathe the testes in cold water at least twice daily. Three months later his sperm count was 60 million and the following month his wife conceived.

The assessment of male fertility by examining the ejaculate can be important but conception is the final proof, and when this occurs in spite of persisting oligospermia it emphasizes that infertility is a symptom complex which cannot be diagnosed on one adverse factor. This may be adequately compensated for by others which are more favourable. It is unjustifiable therefore to introduce emotional stresses by giving a poor prognosis because a seminal specimen is considered to be subnormal. The prognosis can be guarded when necessary while still offering the encouragement which accumulating evidence is proving to be important to both sexes. Russell (1961) recorded 8 pregnancies in spite of counts below 10 million and Swyer (1961) reported 10 patients in a series selected for A.I.H. who conceived without it. Three pregnancies occurred at Oxford in spite of sperm counts not exceeding 2 million. Variations in counts and behaviour in consecutive specimens from the same male have not received the attention they deserve. The laboratory is no more infallible than the clinician.

Postcoital Test

The best indication of male capacity, apart from pregnancy, is provided by the postcoital or Sims-Huhner test, although it is often omitted from infertility investigations as emphasized by Davidson (1961). It avoids the obvious objections to masturbation as a means of producing semen, as well as the danger of misinterpreting a poor

specimen collected reluctantly in this way. Danezis (1963) consistently found a better quality semen in postcoital specimens with a 5–15% higher incidence of oval spermatozoa. A good test establishes that the husband is potent, ejaculates adequate seminal fluid, and has no major anatomical defect interfering with its delivery. It also establishes that the wife permits adequate penetration, has a cervix favourably placed to receive the ejaculate with mucus permitting sperm invasion and survival.

For these reasons the postcoital test should be the first one performed. The optimum time is at the ovulatory phase of the cycle when cervical mucus is most favourable for sperm penetration. According to Marcus and Marcus (1963) it reaches a peak of secretion of 200–700 mg. a day 24–48 hours before the basal temperature begins to rise. A satisfactory test can sometimes be obtained at any time of the month, but a positive test is then more significant than a negative one. Active spermatozoa may be found 2–3 days after intercourse, but 8–12 hours is a convenient and reliable time interval for the test. An excellent result immediately after intercourse, or within a couple of hours of it, may mislead. Davidson (1961) described a patient with secondary infertility and a postcoital test reported as good on three occasions immediately after intercourse, whereas when the test was repeated twice 8–16 hours later sperm invasion was poor. Minor œstrogen deficiency was diagnosed and when the test was repeated a month later after the administration of pre-ovulatory œstrogen the mucus was teeming with progressive spermatozoa and conception occurred during that cycle. Hartman (1962) drew attention to the possible difference between the time spermatozoa remain motile and the time during which they retain their capacity to fertilize the ovum. He considered that the power to fertilize is lost in about half the time motility is retained. Motile sperms have not been found in uterus and tubes longer than 40 hours after intercourse. When cervical mucus is hostile the administration of œstrogen can result in sperm penetration and can double the survival time. The cervical factor has been implicated as the main cause of infertility in from 30–50% of patients in many studies including those of Marcus (1963), Steinberg (1955, 1958), Asplund (1959), Odeblad (1959) and Moghissi and Neuhaus (1962).

The interpretation of the postcoital specimen becomes largely a matter of personal experience but the following points may act as a guide. Three samples are taken, two from the cascade of mucus at the external os and one from the endocervical canal. One from the cascade is allowed to dry and should show typical arborization

without cellular debris at the time of ovulation, indicating a healthy endocervix with adequate œstrogen levels. If ferning is atypical or there is an excess of debris and sperm invasion is poor, the administration of small doses of œstrogen is indicated. The remaining two specimens are examined first under low power with reduced illumination to obtain a general impression of the field and then under high power. A suggested classification is:

Negative. No spermatozoa are seen.

Poor. A variable small number of sluggishly motile or non-motile spermatozoa in the endocervical mucus.

Fair. 1–5 actively motile spermatozoa per high power field.

Good. 6–20 actively motile spermatozoa per field.

Excellent. Clear mucus containing more than 20 actively motile spermatozoa per high power field.

A single test is of value only when positive and a negative test indicates that further investigation is necessary. It should be repeated at the optimum time, day 10–14 of a 28-day cycle, and cultures should be made of the endocervical mucus with sensitivity testing of any pathogenic organisms found. Negative or abnormal tests are due to incorrect timing in relation to ovulation, infected or hostile mucus, oligospermia, azoospermia or poor quality of spermatozoa, anatomical defects of male or female interfering with adequate insemination, and possibly undetermined "lethal factors" as suggested by Masters and Johnson (1961). They demonstrated a lethal factor to spermatozoa in 17 couples, in 15 of whom it was in the vagina and in 2 in ovulatory cervical mucus. The nature of the factor was not determined. In such cases precoital vaginal douching with an alkaline solution, Ringer's or glucose solution may be helpful.

Behrman *et al.* (1960) postulated ABO blood incompatability as a source of antibody formation with antigens carried by the spermatozoa blocked or immobilized by antibodies in the cervical secretion. Whitelaw *et al.* (1962) found no support for this view but Behrman's research continues.

Grant (1958) correlated the appearance of cervical mucus with its content of leucocytes. Clear mucus contains relatively few, whereas a cloudy appearance is associated with many, which if present at ovulation usually indicate endocervicitis. At other times of the cycle heavy leucocytic infiltration does not necessarily imply infection. Grant stated that even with cervicitis the mucus could be temporarily clear at ovulation but remain biologically defective.

In an ideal ovulatory specimen there should be not more than 4 leucocytes in a high power field. Sobrero (1962) and Sobrero *et al.* (1962) made a detailed study of the bacteriology of cervical mucus in 350 infertile women. Organisms most commonly encountered were a hæmolytic *Staphylococcus aureus*, *Ærobacteria Ærogenes*, *Enterococcus fœcalis*, *Streptococcus viridans* and *E. coli*. In more than half the patients there were multiple organisms. Sensitivity tests proved that chloromycetin and furadantin were generally the most effective agents.

Uterine and Tubal Factors

In the study of infertility many widely accepted standards have been simplified until their very simplicity provides a major source of error. Unless they are kept under constant review it will be found that no amount of dogma can conceal their inaccuracy. This would be true if infertility depended on only one factor, whereas the ovum, sperm, tube and endometrium are the basic minimum requiring investigation in the complex syndrome.

Hypoplasia

The diagnosis of genital hypoplasia is commonly made but rarely justified. The only accurate way of measuring the length of the uterine cavity is with a sound but even accurate measurements are not a reliable indication of functional capacity. Still less so are clinical and radiological estimates. If the organ is thought to be small this will usually be less significant than the despair, tension and disturbed function consequent on the woman being told that her genital development is infantile. When menstruation begins at the age of 18 or later there may or may not be some degree of hypoplasia, but this will certainly not be present if the menarche was at 12 or 13 years of age with subsequent regular menstrual cycles. If this general principle were remembered much unnecessary suffering would be avoided.

Mrs. Y., aged 31, complained of primary infertility and was informed by one of Europe's most famous gynæcologists that she had a hypoplastic uterus, was not ovulating, and that pregnancy was impossible.

She had started menstruating at 14 with a regular 5/28 day cycle, and an extreme degree of acute anteflexion made the uterus feel smaller than it actually was. Hysterography (Fig. 52) revealed an intra-uterine polyp and conception followed its removal.

FIG. 52. Acute anteflexion and intrauterine polyp.

Tubal Occlusion

Rubin (1920) made a contribution of great importance with his insufflation test, but its simplicity was dangerous. It was a reasonable assumption that when gas passed, tubes were open, and when it did not they were blocked. Four tubal categories were described:

1. The normal, which accounted for $43 \cdot 2 \%$.
2. The blocked, $26 \cdot 1 \%$.
3. The stenosed, 26%.
4. Tubes showing spasm, $4 \cdot 7 \%$.

This classification summarized the results of insufflation and salpingography, but only time could reveal its prognostic accuracy. The ultimate test of tubal status is whether uterine gestation occurs and the classification implied that conception would be impossible when tubes were blocked, and at least impaired by stenosis or spasm. Rubin (1932) reported that $26 \cdot 8 \%$ of patients with normal tubes conceived compared with $23 \cdot 8 \%$ with spasm and $21 \cdot 6 \%$ with stenosis. Although the results were similar the traditional teaching continued that patients with normal tubal patency had a good

prognosis but in those with stenosed and adherent tubes it was poor. Some patients with apparently blocked tubes conceived, and a study of this group led Rubin to believe that pregnancy would not occur if 3 patency tests were negative. Time proved this to be incorrect. Jeffcoate (1953) reported 25 pregnancies after 3 unsuccessful patency tests and there are many similar references in the literature. Peel (1964) commenting on the difficulty of diagnosing cornual occlusion, referred to patients early in his series on whom he performed tubal transplantation only to find that histological examination of the extirpated portion disclosed a normal lumen. He reported 10 pregnancies after 3 negative salpingograms, adding 3 to the total in an earlier publication (Peel, 1956) and emphasized the need to test patency from the ampullary end at laparotomy before proceeding to transplantation. Even this sometimes failed to demonstrate patency in tubes subsequently shown to be open. Siegler (1963) stressed the importance of examining the excised allegedly blocked segment when operating for occlusion and after years of research into tubal behaviour Stallworthy (1948, 1959) stated that occlusion was more commonly functional than organic in origin. This view carried important diagnostic and therapeutic implications. The incidence of organic damage will vary from community to community, and where pelvic sepsis is common the number of patients with damaged or blocked tubes will be higher but the important fact is not so much the differing incidence of infection as that one observer, by improving his technique, will progressively reduce the incidence of occlusion he previously believed was due to this.

Rocker (1964) studied the anatomy of the uterotubal junction and found the lumen was only 100 microns, with a sharp change of direction in the uterine wall. Increased uterine contractions could compress the lumen at this point. Sweeney (1962) studied 50 uteri and demonstrated that the interstitial portion was straight in only 23 of the 100 tubes and observed that the tube could take a right-angled bend in the uterine wall. This helps explain the difficulty of demonstrating patency at the uterotubal junction.

Radiological diagnosis of uterine irritability is not difficult as illustrated in Fig. 53 but this does not justify excluding organic occlusion, although irritability is usually functional and causes temporary occlusion. Hartman (1962) described the uterotubal junction as the portal to the uterus and under ovarian hormone control. When there is a predominance of œstrogenic hormone it is kept contracted, and relaxes to allow the fertilized egg to pass when progesterone comes into action. A practical implication is

(a)

(d)   (c)   (b)

FIG. 53. Uterine Spasm.
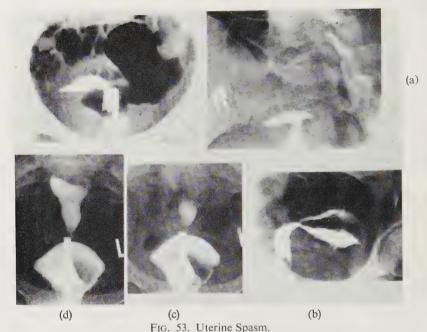
FIG. 53a illustrates the hysterogram of a patient aged 34 complaining of
    many years primary infertility who was told that both tubes were
    blocked and was given a hopeless prognosis. Aged 39 she requested
    a second opinion, produced the original hysterogram film, was
    found to have a fibroid, and when it was explained that all her
    X-ray demonstrated was an extremely irritable uterus which could
    be due to the fibroid she conceived the following month before
    further tests were performed.
    b illustrates a double tuberculous uterus.
    c demonstrates extreme irritability and bilateral cornual occlusion
    due to multiple fibroids.
    d demonstrates irritability and occlusion in the absence of
    organic pathology.

that the possibility of a negative insufflation or radiological test is
greatest in the pre-ovulatory phase, which is when it is usually
performed. The injection of progesterone some hours before
examination has been suggested as possibly more effective than
spasmolytic drugs.

Whereas in most patients functional occlusion is a primary and
temporary manifestation, in others it is secondary to uterine or
tubal pathology.

The lesson to be learned from these illustrations is that whereas
10 years ago the functional element in tubal behaviour tended to be

overlooked, there is a danger today that it may be overemphasized and the fact be forgotten that uterine and tubal irritability may be caused by organic disease.

Tubal Surgery

Three alleged recent advances in surgical technique reviewed by Peel (1964) are:

1. The use of a reamer advocated by Green-Armytage (1960) and Shirodkar (1960).
2. The use of polythene rods.
3. The administration of cortisone locally and systemically.

He stated that none of these accomplished the results claimed for them. For example, Puigmacia (1960) reviewed 726 operations performed by surgeons in different parts of the world who answered a questionnaire. The pregnancy rate was $27 \cdot 3\%$ when polythene rods were used and 27% when they were not. Palmer (1960) had a success rate of 36% without the use of polythene rods and Moore-White (1960) achieved the excellent figure of 56% without them. Peel concisely summarized the present position of tubal surgery as follows:

1. When tubes are not organically damaged but have been tied either deliberately at sterilization or inadvertently during an operation such as myomectomy the results of operation in competent hands are likely "to be reasonably good".
2. Postabortal obstruction of the interstitial portion by infection with a normal distal tube is extremely rare and great care is necessary to exclude cornual spasm.
3. The results of operating on tubes obstructed by organic disease after generalized salpingitis are uniformly poor.

It was in this last group, least favourable for surgery, that Moraes and Peano (1958) reported most encouraging results, including pregnancy, following the local instillation of hydrocortisone and antibiotics.

Tubal and Endometrial Tuberculosis

Rabau (1952) reported the first pregnancy following treatment of endometrial tuberculosis by chemotherapy. Stallworthy (1952) described safe techniques in the surgery of pelvic tuberculosis prior to the discovery of streptomycin, and indicated the role they would

continue to play in association with medical treatment. There has been considerable progress since then but it appears from the literature that conflicting views are still held on the question of treatment. Knaus (1962) advocates surgery, but most writers favour drug therapy, at least in the initial attack. These views may not be as conflicting as they at first appear because the attitude to treatment is influenced by the extent of pelvic disease. Whereas it would be unjustifiable to operate on a young woman in whom endometrial tuberculosis was diagnosed in the absence of clinical signs, there would be less disagreement over the role of surgery in an older woman with adnexal tuberculous masses. There are parts of the world in which this is the usual clinical picture (Fig. 54). Nonetheless, chemotherapy is the method of choice and will in many doubtful cases make surgery unnecessary.

In 1942, when unsuspected endometrial tuberculosis was first diagnosed at Oxford in 5 patients after biopsy, one of us (J.S.) wrote to several senior colleagues for advice on treatment because we knew even less about the condition then than now. One of those approached was the late Mr. Victor Bonney. The relevant section of his reply, dated January 9th, 1943, almost exactly 23 years ago, is
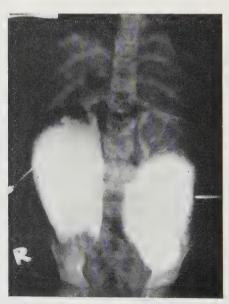
FIG. 54. Bilateral Tuberculous Pyosalpinx.

reproduced partly for historical interest and partly as an example of the encouragement a senior teacher can give to a young pupil. The letter reveals his active interest and original thinking, while at the same time demonstrating how much progress has been made since then.

What you tell me is exceedingly interesting and I hope you publish It. Up to now Tb. infection of the endometrium has been held a very rare occurrence. How many biopsies did you have to do to get 5 cases?— also you say there were no signs in any of them of Tb. salpingitis or Tb. elsewhere! How does the infection get in? Seeing that the surface of the endometrium is shed monthly it seems unlikely from the uterine surface, but it is an odd situation for blood infection. As regards treatment I would have thought abdominal curettage more efficient than curetting from below. Hysterectomy seems too drastic unless the disease has got into the uterine wall and even then it could be excised if sufficiently local. Could radium be applied in great strength for a very little while to kill the bacilli and spare the ovaries? But is Tb. susceptible to radium? This could easily be tried in the laboratory—let me hear further. My best regards.
P.S. It would be interesting to inoculate guinea pigs with vaginal secretion and see if any of them develop Tb.

A joint sub-committee appointed by the Royal College of Obstetricians and Gynæcologists and the British Tuberculosis Association investigated this disease and its response to medical treatment. The first trial consisted of a controlled study of streptomycin and P.A.S. administered for 3 months and the results were reported by Sutherland (1954, 1957a and b). The second trial investigated the relative merits of streptomycin and P.A.S. combined, and streptomycin and isoniazid combined, and the results were reported by Sutherland (1958). In summary, chemotherapy proved capable of curing the disease in 80–90% of patients, and the combination of streptomycin and isoniazid was preferable to streptomycin and P.A.S. because of less drug reaction. In the meantime a much wider experience was accumulating of the response of tuberculous lesions to modern drugs in other fields of medicine, particularly in chest diseases. Modern views on treatment acceptable to the British Tuberculosis Association have been given by Crofton (1960). At least 15 g. of P.A.S. daily, or 200 mg. of isoniazid, are necessary to prevent streptomycin resistance. Medical Research Council trials have shown that it is safer to give 20 g. of P.A.S. daily, but this causes a high incidence of gastro-intestinal intolerance and 15 g. is accepted as a better dose. To avoid isoniazid resistance 10–12 g. P.A.S. daily is sufficient.

The isolated mycobacterium is tested for drug sensitivity and while this is being done treatment should consist of streptomycin 1 g. a day P.A.S. 5 g. three times a day, and isoniazid 100 mg. twice daily, or three times daily according to individual preference, as discussed by Crofton for patients under the age of 40. Therapy is later adjusted according to sensitivity, and if there is isoniazid resistance streptomycin 1 g. a day and P.A.S. 15 g. a day should be continued, while if there is P.A.S. resistance streptomycin and isoniazid are indicated. Fortunately in most patients the mycobacterium is sensitive to isoniazid and P.A.S. so that treatment can be continued with these two drugs alone in doses of 200 mg. and 10 g. daily respectively for a minimum period of 6 months after all evidence of infection has disappeared.

Genital Tuberculosis and Pregnancy

The main justification for medical treatment of genital tuberculosis in young women is the prospect of cure being followed by pregnancy. The prognosis is obviously influenced by the condition of the tube prior to treatment. Whereas even in advanced fibrocaseous disease it not uncommonly remains patent, its physiology is disturbed and if conception occurs ectopic gestation is probable, although successful uterine pregnancy is not impossible.

Mrs. C. had tubal and endometrial tuberculosis proven bacteriologically. After treatment there was a residual hydrosalpinx on the right side and radiologically a typically tuberculous left tube. Conception occurred and progressed uneventfully to produce a healthy infant.

This patient was admittedly fortunate and the prognosis improves with the absence of physical and radiological signs of tubal damage. Nonetheless, there are few major organic ætiological factors in infertility with a better prognosis after treatment than genital tuberculosis without adnexal masses. Snaith and Barns (1962) reported a pregnancy rate of 12%, with 20% when tubes were patent, results similar to those published by Halbrecht (1957). Stallworthy (1963) reported 18% of infertility patients with genital tuberculosis conceived after treatment, and 10% gave birth to living children. There were 9 successful pregnancies in 17 conceptions with 5 ectopic gestations and 3 abortions. Ryden (1958), reviewing the experience of multiple authors, assessed the overall conception rate following treatment at 4%, but when tubes were patent the incidence rose to 30%. Records have been collected from the literature, and by personal communication, of a total of 121 successful pregnancies

following the treatment of this disease (Stallworthy, 1963) although in some cases it was not stated whether bacteriological proof of infection was obtained. Other authorities including Knaus (1962), Schaefer (1959) and Olli Ylinen (1961) are less optimistic concerning the prospect of pregnancy.

Schaumann Bodies and Tuberculosis

Doubt has been thrown by Campbell *et al.* (1964) on the ætiology of granulomatous salpingitis with Schaumann bodies and crystalline inclusions. In 1958 they drew attention to oil granulomata of the uterus, tubes and pelvis and the danger of these lesions being caused by mineral oil lubricants used on dilators being forced through the uterus and tubes, a complication which could be avoided by using hollow dilators. Four cases of granulomata of the uterus detected

(a)   (b)   (c)
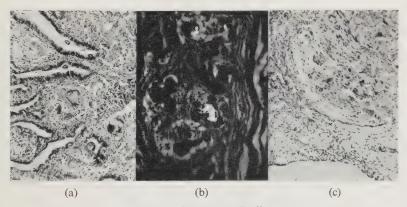
Fig. 55. Schaumann Bodies.
(a) Granulomatous Salpingitis.
(b) Crystalline Inclusions.
(c) Granulomatous Nodule.

at the Ottawa General Hospital from 1961–63, and 5 of apparently similar pathology in the tube encountered from 1957–62 were reviewed. We are indebted to Campbell for the illustrations in Fig. 55. Granulomatous salpingitis with Schaumann bodies and crystalline inclusions were believed to be non-tuberculous and possibly a manifestation of an immune reaction, even to spermatozoa. As an addendum to their paper they recorded that in a final check on the possibility of an infective basis to these lesions further sections of a fallopian tube were studied after Ziehl-Neelson staining and two

acid-fast bacilli resembling mycobacterium tuberculosis were detected. One swallow does not make a summer but further research is necessary and bacteriological proof should be sought whenever possible.

Pregnancy

One basic relevant problem requires further research—whether conception can occur in the presence of active endometrial disease. Most authorities deny this possibility. It should be remembered, however, that genital tuberculosis presents itself in many ways, and the diagnosis is often made during infertility investigations in patients who feel perfectly well. There are many causes of infertility and most infertile women are not suffering from tuberculosis. It may well be that some fertile women are, but the disease is not diagnosed because investigations are unnecessary. It seems illogical to conclude that all women with genital tuberculosis are sterile because the disease is found in some who complain of infertility. If tubes are not disorganized there would seem to be no reason why a woman with genital tuberculosis should be infertile. Fisher (1952) reported a case of tuberculous endometritis diagnosed 12 days after an abortion at 20 weeks. Pregnancy and the endometritis must have coexisted. Stallworthy (1963) reported 3 patients with bacteriologically proven tuberculous endometritis and histories suggesting or proving the coexistence of pregnancy and infection. Further research is indicated, but it is apparent that active infection in the endometrium is not an absolute bar to conception.

Uterine Adhesions or Synechiæ

A young para 1 was admitted to hospital bleeding from a missed abortion and the uterus was evacuated. There was neither excessive hæmorrhage nor shock. Following this she developed amenorrhœa and sought advice for infertility. Hormone studies gave negative results and the probability was overlooked that with this history the explanation could be intra-uterine traumatic adhesions (Fig. 56). The patient subsequently conceived.

The condition has been recognized sporadically since the beginning of the century by such famous surgeons as Wertheim, Halban and Veit, but fresh interest was aroused when Stamer (1946) pointed out that it is not uncommon as generally believed. He reviewed 37 cases in world literature from 1894–1933, including 20 described in 1927 by Bass, and reported a further 24 seen personally by him

FIG. 56. Uterine Adhesions. Central oval area due to adhesions. Intravasation at one cornu.

at Copenhagen in only 2 years. He believed the causal factor was excessive zeal in curetting the postabortal and puerperal uterus with removal of basal decidua and myometrium.

Asherman (1948) disagreed with this explanation and described the syndrome of amenorrhœa, or recurrent staining, with or without uterine pain, following complicated labour or abortion as due to trauma and stenosis at the internal os. Although ovulation occurs, the endometrium remains inactive and hæmatometra does not

develop. No explanation was suggested for this. He reported 29 cases, 11 after postpartum curettage and the remainder following manual removal of the placenta or as a delayed complication of abortion. He suggested amenorrhœa traumatica or atretica as a suitable name for the syndrome and recommended passing a sound 6 weeks after postpartum and postabortal curettage or manual removal of the placenta. Hegar dilators were passed to size No. 8 if stenosis was demonstrated. Because the incidence was highest when curettage was performed approximately 2 weeks after delivery or abortion, Asherman believed that the complication could be avoided by removal of retained placental tissue immediately after delivery and avoidance of curettage at the dangerous time 10–14 days later. He advocated packing the uterine cavity with penicillin gauze for 24–48 hours if curettage was necessary. In 1950 Asherman reported the same syndrome with clinical findings similar to those described by Stamer, with trauma responsible for intra-uterine adhesions. Sometimes a sound could not be passed because of complete stenosis, but when it could and the uterus was studied radiologically the picture could be confusing. Differential diagnoses are polypi, endometrial and myometrial tuberculosis, submucous fibroids and septa, and air bubbles. If adhesions are confined to the region of the internal os the passage of a sound and dilators restores menstruation to normal, but when they are extensive throughout the uterine cavity it may be impossible to break them in this way and it is easy to perforate the uterus. In such cases both Asherman (1950) and Maggioni (1963) advise laparotomy, hysterotomy, and division of adhesions under vision, and report successful pregnancies following this. Maggioni found 8 patients with traumatic synechiæ in 142 women investigated for infertility by hysterosalpingography. He operated on 6 and pregnancy followed in 3. Asherman passed a soft catheter through the cervix and left it in the uterine cavity for 3 days. A small Foley catheter distended with 3–4 ml. of sterile fluid is useful after the adhesions are divided and allows the cavity to be irrigated with an antibiotic solution as recommended for tubal occlusion by Moraes and Peano (1958). They use streptomycin 1 g. with 25 mg. of hydrocortisone acetate in local anæsthetic solution.

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CARCINOMA OF THE CERVIX

*"Cancer of the uterine cervix is now regarded as a
preventable disease."*

This statement by a World Health Organization Cancer Committee
in 1963 was a milestone in the history of uterine cancer. Whereas
few women survived from this disease 70 years ago, 46·3% of 117,613
patients treated between 1948–57 were alive and well 5 years later.
The figure rose to 48·5% with 61,776 patients treated from 1953–57.*
In some hospitals the results are considerably better than this but
even more important is the fact that where existing facilities are used
women now living need never die from carcinoma of the cervix.
This is a concept of stupendous importance and presents the pro-
fession as well as the public with a challenge which cannot be ignored.
If it is accepted, posterity will regard the virtual elimination of cancer
of the cervix as one of the great triumphs of preventive medicine,
and will look back to the twentieth century to study how it was
accomplished.

It has been estimated that half a million women in the world are
suffering from carcinoma of the cervix. This emphasizes both the
size of the problem and the urgent need for a co-ordinated and
efficient prophylactic and therapeutic attack. In the British Isles,
where 11% of deaths from malignant disease in women are due to
uterine cancer, there are approximately 3,500 deaths a year from
carcinoma of the cervix. This means that every $2\frac{1}{2}$ hours a patient
dies.

The new classification and staging of uterine cancer (Appendix A),
adopted by the International Federation of Obstetrics and Gynæ-
cology, came into operation on January 1st, 1962. Three groups
are described:

1. Invasive carcinoma of the cervix (Stage 0).
2. Carcinoma of the cervix (Stage 1–4).
3. Carcinoma of the corpus (Stage 0–4).

* *Annual Report on the Results of Treatment in Carcinoma of the Uterus and
Vagina* 1964. Ed. H. L. Kottmeier.

According to the Registrar-General (1963), carcinoma of the cervix has twice the incidence of carcinoma of the corpus, but inaccurate certification is probably responsible for an error in this assessment. Corpus carcinoma is increasing with longevity, and there is now little difference between the number of patients treated for this disease and cancer of the cervix. An international assessment cannot be made because of lack of information. In the Annual Report, Volume 12 (1961), 105 institutions furnished data on carcinoma of the cervix but only 36 reported on corpus carcinoma. In Britain the 1961 Report of the South-West Region Cancer Bureau, with 100% registration of malignant disease, analysed 2,742 cases of uterine cancer registered from 1950–56. Corpus carcinoma accounted for 1,275 (46·5%) and cervical cancer for 1,467 (53·5%). In 1960 the corresponding numbers were 277 and 273, giving an incidence per hundred thousand of the female population of 18·5 and 18·2. The Oxford Regional Cancer Survey records the same trend. A consequence of recent advances in the prevention, detection, and treatment of cervical cancer is that both its incidence and mortality will fall, while carcinoma of the corpus will become both relatively and actually more common unless the increasing use of progestogens (Chapter 7), or some new development, arrests its progress. Kistner (1959) has studied the effect of progestins on hyperplasia and carcinoma-in-situ of the endometrium and believes that the use of these new preparations may prevent the development of corpus carcinoma.

Carcinoma of the Cervix Stage 0

This is the term used in the international classification. Broders (1932) gave it the descriptive name of carcinoma-*in-situ*, and synonyms are "pre-invasive carcinoma", "intra-epithelial carcinoma", and "Ca0". It has also been described as Bowen's disease of the cervix. Considerable space is given to a discussion of Stage 0 and associated lesions because failure to detect them will constitute an avoidable factor of increasing importance in relation to uterine cancer. It is necessary to recognize both the contribution that new techniques have made and their limitations.

In 1910 Rubin described 3 patients with "incipient carcinoma of the cervix". Reference to his paper shows that these were in fact Stage 0 lesions. Schottlaender and Kermauner (1912) with whom he had worked drew attention to the same condition, as did Schiller in 1927. An extensive literature has accumulated with increasing

recognition of the fact that a Stage 0 lesion can be present on an apparently healthy cervix. Younge *et al.* (1949) found an incidence of 1.2% in apparently benign cervices biopsied after a positive Schiller test, while Gusberg (1953) demonstrated the lesion in 1.6% and basal cell hyperplasia in 1.8% of 1,000 healthy-looking cervices.

Recent developments provide a practical basis for the prevention of cervical cancer and are based on two important discoveries. They are:

1. The ætiological significance of Stage 0 lesions in invasive carcinoma.
2. The use of screening techniques applicable to healthy women to select those at increased risk because of invisible changes in cervical epithelium. These techniques are:
   (*a*) Schiller iodine test.
   (*b*) Gynæcological cytology.
   (*c*) Colposcopy and colpomicroscopy.
   (*d*) Biochemical assay.

Stage 0 Lesions and Invasive Carcinoma

Te Linde and Galvin (1944, 1949) recognized both basal cell hyperplasia and carcinoma *in situ* as pathological entities. Te Linde paid tribute to the contributions of Schiller (1933, 1936, 1938) who first conceived the idea that intra-epithelial changes could be the beginning of invasive cancer. Retrospective studies at Johns Hopkins Hospital involved the re-examination of preserved biopsy specimens taken years before invasive carcinoma developed. It became evident that some women with carcinoma of the cervix had pre-existing Stage 0 lesions but others with Stage 0 changes did *not* develop invasive cancer. Te Linde and Galvin established that Stage 0 lesions and microinvasion were often associated as when they demonstrated invasion in 15 of 16 cervices removed by hysterectomy for Ca0. This was the more interesting in that some illustrations published by Galvin and Te Linde (1949) as typical of Stage 0 changes, selected from the 16 patients referred to above, show extensive basal cell hyperplasia with surface layers reasonably well defined. Nonetheless, microinvasion was found, which supports the view of Younge *et al.* (1949), Gusberg (1953), and others that basal cell changes can be a stage in the progression from normal epithelium to carcinoma.

The ætiological significance of epithelial dysplasia was further clarified by Nielson (1952) and Petersen (1956) from the "Radium

Centre" in Copenhagen. Stage 0 lesions were diagnosed in 212 patients and 127 were left untreated and followed carefully, 104 of them for at least 5 years and 38 for a minimum of 10 years. Cancer of the cervix developed in 33 % within 9 years and in 4 % within 1 year. Kottmeier (1956) reported invasion in 15 of 31 patients observed, and recorded 1 in whom cancer developed $17\frac{1}{2}$ years after the pre-invasive lesion was first detected. Boyes *et al.* (1962) suggest that probably the correct incidence of invasion developing in patients with Stage 0 lesions of the cervix is 60%, with a time interval of 13–20 years, but they emphasize that the data available are insufficient to guarantee this assessment being statistically reliable. The evidence accumulated from many sources establishes such a high correlation between CaO and cancer that CaO must be regarded as pre-malignant. A woman with a stage 0 lesion of the cervix lives under the sword of Damocles. It may never strike, but the risk of it doing so increases with each passing year. Petersen adopted the view that because there is no proof that all Stage 0 lesions progress to invasive cancer their radical treatment is not justified. Much depends on what is meant by radical treatment. Total hysterectomy would be considered radical if there was no clear indication for operation. Anderson (1959) stated that the biopsy necessary for diagnosis is often the only treatment required and this wise observation has great practical importance. While the Copenhagen study does not prove that all carcinoma *in situ* progresses to invasion, neither does it prove that it does not. The important point is that a woman with a Stage 0 lesion is at considerably greater risk, but the extent of this and the factors, other than time, which may influence it are at present not known. Kirchhoff (1964) believes that even the social status of the patient affects tissue response. Nielsen's study is sometimes quoted as proving that 30% of women with CaO develop invasive cancer, but this is an incorrect interpretation of his results, as illustrated from the same material by Petersen and Wilklund (1959) who recorded that by the 14th year cancer developed in 18 of 52 patients (35%). Koss (1961a) studied cervical epithelial instability in approximately 100 women at the New York Memorial Hospital and found that lesions became malignant in 25%, remained stationary in 50%, and regressed in 25%. Anderson (1959), on the other hand, believes that it is doubtful whether changes typical of a Stage 0 lesion are reversible. New knowledge of intracellular disruption in CaO, described later, supports this belief.

Boyes *et al.* (1959, 1960, 1962) tested the truth of these observations by adopting the logical approach that if Stage 0 lesions are

pre-malignant and are detected and treated effectively the incidence of cervical cancer should fall. The extent to which this can happen is not yet known (and would not necessarily be known even if it were possible to eradicate all carcinoma *in situ*) because although it is established that invasive cancer may be preceded by Stage 0 lesions it has not been proved that this always happens. Cellular biochemical, biophysical, enzymal and morphological changes occur during the transition of a normal cell to its malignant counterpart and there may be intermediate phases on which the fate of the cell, and the patient, depend. There may or may not be a point of no return in the intracellular revolution. Years may be required to complete these changes but it is not known with what rapidity they can occur, nor what factors influence their progress. They may sometimes be relatively transient, and if so new techniques will be required to detect all patients at risk. Research on these basic fundamentals is likely to throw a clearer light on the whole complex problem of cancer.

Boyes *et al.* (1962) set out to screen the female population of British Columbia. They examined approximately one-third of the women aged 20 and over and treated Stage 0 cervical lesions. Clinical carcinoma of the cervix was reduced by 30·6% between 1955–60, its incidence falling from 28·4 per hundred thousand to 19·7. By 1963 it was 15 per hundred thousand.

The behaviour of Ca0 and its relation to cancer of the cervix may be summarized as follows, with the admission that some important questions remain unanswered.

1. It can precede invasive cancer.
2. There may be an interval of 20 years or more between the first appearance of the one and the development of the other.
3. Stage 0 lesions and invasive cancer can coexist.
4. They may not progress to invasion and possibly may sometimes regress.
5. They can be single or multiple, closely associated, or widely separated.
6. They do not metastatize and do not recur, but a new lesion can develop and, when multi-focal, one may be removed while the other is left.
7. Carcinoma of the cervix may possibly develop without pre-existing Stage 0 changes detectable by tests at present available.

Sufficient of the jigsaw has now been assembled for a picture to be recognizable. Epithelial instability of a localized focal pattern

can develop for no apparent reason in a cervix which looks perfectly normal, as well as on one which is lacerated, infected, or eroded. It can progress from basal hyperplasia to anaplasia to Ca0 and finally to invasive cancer. Total removal of these areas before invasion begins liberates the patient from an otherwise ever-present risk of cancer, and when this is done on a considerable scale in a community the incidence of cancer of the cervix falls. This raises important questions concerning the incidence of these lesions in apparently healthy women, methods of detecting them, and how best they may be treated.

Incidence of Stage 0 Lesions

These, like invasive carcinoma, have a variable racial incidence. Anderson (1953) stated that they are six times more common among non-Jewish women than among Jewesses, while Stern (1959) found only 2 cases in a study of 4,072 Jewesses in Los Angeles, a rate per thousand of 1·49 as compared with a general incidence in that area of 4. Negresses in the same survey had an incidence of 15 per 1,000, while Christopherson and Parker (1960) found the rate higher with Caucasian women than with negresses. It was 1·45 per 1,000 in over a million Chinese women as reported in the *Journal of the International Federation of Gynecology and Obstetrics* (1964), **2,** 177. The explanation of these variations is not simple. It does *not* follow that they are due to racial susceptibility, they could be related to social and economic status. The higher incidence of carcinoma in women living in relative poverty and unsatisfactory hygenic conditions has been described by Lawson (1957) and by Rao *et al.* (1959). Personal hygiene affecting both males and females is important and the higher incidence of cervical cancer in syphilitic women has long been established. The possible role of circumcision is discussed in Appendix B. Baird (1965) stated that women in social class V, when compared with the wives of professional men, had nearly 20 times the incidence of carcinoma of the cervix, the figures per 10,000 being 5·6 and 0·3 and in grand multiparæ 10·1. Early marriage and multiparity placed a woman in the high risk category and Stage 0 lesions developed 10–19 years after the first intercourse. The pre-invasion/invasion ratio decreased with age, a fact emphasized by Petersen (1956) and Carter *et al.* (1956). Until the age of 40 Stage 0 lesions are more common than invasive carcinoma, but after 40 the incidence falls steeply. Wynder (1955) quotes Rojel of Copenhagen as stating that prostitutes have a higher incidence of cancer

of the cervix. By contrast, Gagnon (1950) was unable to trace one case in the records covering a period of over 20 years in a community of nuns. Towne (1955) found only 3 patients in her 21-year survey of another religious community with an average annual population of 10,000 women. Childless married women have a rate twice as high as unmarried ones. The risk is increased by marriage and sexual intercourse before the age of 20. These facts highlight those sections of a community at greatest risk.

Cellular Changes

A novice at cytology can recognize the difference between normal squamous cells and the giant polymorphic cells with large hyper-chromatic nuclei and irregular chromatin distribution characteristic of cancer. An expert of great experience can have difficulty in deciding on cells with border-line changes, but a patient is safer with highly malignant-looking cells confined to a focus of carcinoma-*in-situ* than with well-differentiated ones which have penetrated the basement membrane to invade underlying tissues. The point on which possibly the ultimate solution of the cancer problem depends, concerns what is happening within a cell to produce this meta-morphosis. Whatever these changes may be they can take years to progress until they cross that final narrow dividing line which differentiates an abnormal benign cell from a well-differentiated malignant one.

Readers interested in exploring new techniques of investigating intracellular structure and behaviour by electron microscopy, histo-chemistry and histophysics are referred to the following publications:

1. *Electron Microscopy*
   Coman *et al.* (1955); Howatson and Ham (1957); Lubel *et al.* (1959); Sirtori and Morano (1963).
2. *Histochemistry*
   McManus and Findley (1949); Foraker and Denham (1957); Pitot (1961); Willighaghen (1961).
3. *Histophysics*
   Mellors *et al.* (1952, 1953).

Smithers (1956) stated that a final solution of the cancer problem was impossible because it is part of the nature of complicated organisms that they cannot maintain their organization indefinitely. He thought it would be strange if cancer did not exist, and believed that success in its clinical handling depended on more effective

prevention, or the postponement of tissue disorganization. Sirtori (1963) drew attention to the similarity on electron microscopy of nuclear and cytoplasmic changes in senile and malignant cells. Emerson Day (1961) supported these views with the startling observation that malignant tumours account for 5·2 deaths in 100,000 women under the age of 20, but in 1,388 over the age of 80. Age may itself be carcinogenic and the cell, like the individual of whom it is part, may vary within a wide range in its response to the passing years. The woman of 60 may look 40 and the woman of 40 may be grey and aged. Research into the details of intracellular ultrastructural changes may reveal not only why this is so but throw light on the riddle of cancer itself.

Boddington *et al.* (1960, 1965) and Spriggs (1962*a* and *b*, 1964) have given an exciting glimpse of some of the changes taking place within the cell during its transition from the normal to the malignant state. Whereas in the former the chromosome pattern is orderly as described in Chapter 6, a revolution takes place affecting the genetic material when changes occur which lead to cancer. Spriggs took biopsy material from pre-invasive and invasive cervical cancer for special preparation, crushing and chromosome study. The normal chromosome pattern was altered with variation from cell to cell to such an extent that no basic arrangement was recognizable. This affected the size, shape, structure and number of chromosomes, which could be euploid or aneuploid (Appendix 1, p. 279). It is as though within the area of dysplasia a battle rages to determine which type of abnormal chromosome pattern can gain mastery to produce a dominant cell line or clone (Fig. 57). In the cells of invasive carcinoma the chromosomes, usually aneuploid, are again abnormal, but there is now some semblance throughout the cancer of a pattern which is constant for that particular growth, not in relation to its epithelial type but to the patient in whom it arose. In other words, the chromosome arrangement in the tumours of 2 women with squamous cell carcinomas need bear no relationship one to the other. Measurement by micro-spectrophotometry of the deoxyribonucleic acid in the nuclei of cells in Stage 0 lesions, when correlated with normal cells, supported the findings of Spriggs and Boddington in reference to chromosomal abnormalities (Reid and Singh, 1961). Steele, Manocha and Stich (1963) found high but variable DNA values in 12 patients with Stage 0 lesions, and histological abnormalities of cell division in carcinoma-*in-situ* have been reported by Moricard (1953). Intracellular disruption in the pre-malignant cell may be responsible for the histochemical changes described by
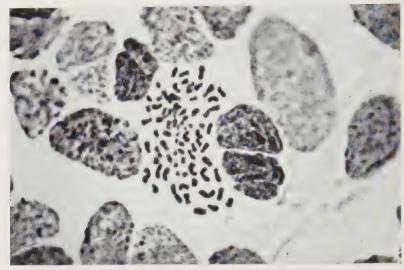
Fig. 57. Orcein-stained squash preparation from a cervical biopsy of caO, photographed with phase contrast. A hypotetraploid cell is seen in metaphase.

Odell and Burt (1950), Fishman *et al.* (1950, 1951, 1954), Lawson (1959) and Nixon *et al.* (1962) and an enzyme screening test based on this work has been devised by Bonham (1964).

Richart (1964) cultured cells from abnormal cervical epithelium in 5 patients. Three had dysplasia, 1 had carcinoma-*in-situ*, and the 5th had microinvasion and all chromosomes were apparently normal. This is difficult to reconcile with the weight of evidence indicating chromosomal aberrations with epithelial dysplasia unless it be that abnormal cells did not grow on culture.

Screening Techniques

These recognize changes before the finger or eye can detect them. Certain guiding principles applicable to all methods are important because of medical and legal implications. They are:

1. A positive screening test does *not* diagnose cancer. It selects those patients who require further investigation.
2. A negative screening test does *not* exclude cancer.
3. Certain tests not only demonstrate the need for further investigation but indicate suspicious areas.

Note: Biopsy is always necessary to establish the diagnosis.

Schiller Test

This is simple, cheap and effective, but is now seldom used. A great advantage is that it is universally available and a general practitioner in his surgery, or a medical technician in Africa, can use it without expensive equipment or facilities for cytology. Normal cells of the ectocervix are rich in glycogen and stain brown with iodine solution. As the patient ages the epithelium becomes thinner and its glycogen content decreases so it stains less deeply and after the menopause may be pale yellow. Benign and malignant dysplasic lesions fail to stain because glycogen is absent or present in small quantities. Younge (1957, 1965) repeatedly advocated using the Schiller test and stated that it was as effective as cytology in drawing attention to dysplasia. He defined a healthy cervix as one covered entirely with squamous epithelium of normal colour distal to the opening of a cervical canal of normal diameter. Its epithelium should stain uniformly dark brown after gentle cleansing and the application of iodine solution.* This is equally true of the nulliparous, parous, or lacerated but healthy cervix. When any change in colour is seen distal to the cervical canal *the cervix is abnormal and must be investigated.* He summarized his views by stating that careful annual clinical examination, with the knowledge of what should be considered normal and what abnormal is still the best method of preventing or detecting carcinoma of the cervix. Unstained benign epithelium is found in hyperkeratosis, parakeratosis, erosions, atrophy, abrasions or traumatic ulceration. Endocervical glandular epithelium also remains unstained, hence the attention given to recognition of the normal lower limit of the canal. Failure to stain constitutes a positive Schiller test. Younge *et al.* (1949) confirmed Stage 0 lesions in $1 \cdot 2 \%$ of patients by biopsy of these areas.

Tetracycline Fluorescent Test

Loo *et al.* (1957) and Rall *et al.* (1957) demonstrated that tetra-cycline and its associated compounds localize and persist in tumour tissues, imparting a yellow fluorescence in ultra-violet light. Berk (1963) used this to detect gastric carcinoma. A total of 3 g. was given in 150 mg. doses 4 times daily and gastric washings were examined under ultra-violet light. If there was a fluorescent yellow staining the test was positive. Koss (1961) reported 6 Stage 0 lesions which

* Lugol's iodine (Liquor Iodi Compositus U.S.P.) is iodine 5%, potassium iodide 10% in water. Gram's solution is 1 g. of iodine and 2 g. of potassium iodide in 300 ml. of distilled water. Schiller's iodine is 1 g. of iodine and 4 g. of potassium iodide in 300 ml. of water.

regressed after the use of tetracycline suppositories, indicating that the antibotic may have a therapeutic effect. More research is needed on this subject.

Cytology

Vaginal cytology is not a recent advance, although its application to cancer detection has become increasingly important. It is based on the fact that epithelium exfoliates its superficial cells and the rapid growth of tumours accelerates this process. Stockard and Papanicolaou (1917) used vaginal smears to study the œstrous cycle of guinea pigs. MacCarty *et al.* (1933, 1934) observed immature cells in vaginal smears, but Papanicolaou (1928, 1941, 1942, 1946) was the first to detect malignant cells. In Britain, Dudgeon and Patrick (1927) studied cells removed from the surface of cut tumours and Ayre (1947, 1954) devised the spatula technique to prepare cervical smears.

Diagnostic Errors

McLaren and Attwood (1961) compared the Ayre technique with vaginal fluid aspiration and in 1,500 antenatal patients found 4 Stage 0 lesions using a spatula but only one by aspiration. In 4,000 gynæcological examinations 13 Stage 0 lesions were detected by the spatula technique and 9 by aspiration, but with clinically detectable carcinoma the results were reversed. The aspiration test was positive in 33 out of 34 patients and review of the negative slide revealed an error of interpretation. The spatula is recommended for routine screening, but gives an error of approximately 10% with clinical cancer, a point of considerable medico-legal importance (Chapter 9).

Technique

Lubricants on examining fingers can spoil the quality of a smear, so before a vaginal examination is made the cervix is exposed; the Oxford Coldlite* instrument illuminated by battery or main supply is ideal for the purpose (Fig. 58). During menstruation blood should be removed with a swab before using the spatula. The longer of the two wings is inserted into the external os and with firm pressure the spatula is rotated through a complete circle. It is then stroked over a clean slide to give a thin evenly-distributed layer of the collected material. The patient's name or number is engraved with a diamond cutter on a plain slide, but details can be written with a

* Obtainable from Vann Bros. Ltd., 63 Weymouth St., London, W.1.

FIG. 58. Oxford Coldlite Speculum.

hard pencil on one with a frosted end.* The slide is placed imme-
diately into a jar of fixative, and, if there is more than one, each
should have a large paper clip attached. These separate the slides,
lessen the danger of transferring cells, and make removal easier.

Fixative

Papanicolaou originally used equal parts of alcohol, acetic acid
and chloroform to give fixation in 1 minute. Longer exposure
reduces staining properties. The acetic acid determines rapidity
of fixation and if omitted from the mixture the slides can be left for
several days without over-fixation. He later used an ether/alcohol
mixture which fixes the slide in approximately 10 minutes. It does
not deteriorate if left longer. Way (1963) uses ethyl alcohol and
ether in equal parts but this is an explosive mixture demanding
caution. Fixed smears can be sent dry for staining and interpretation
and Way advises packing them in soft paper and cotton wool.
Transfer in fixative is better when possible.

* Supplied by Chance Ltd., Smethwick, Birmingham, 40.

For processing and staining techniques readers are referred to standard works on laboratory procedures. A warning is necessary concerning the interpretation of cervical cytology in the presence of infection. Holtorf (1961) examined 1,612 women suffering from trichomonad infection and found minor changes in the cells of 25%. There was an increase in nuclear size with multinucleated cells but the chromatin pattern was normal. In 2% of 739 examinations changes resembled those in cancer. Vaginal infection is usually apparent and should be treated before tests are made. Attwood (1965) reported similar changes in patients using contraceptive pills. For the interpretation of slides readers are referred to Papanicolaou's "Atlas of Cytology" or "Cytology Diagnosis of Cancer" by Ruth Graham.

Cervical Smear

To speak of smears is now accepted practice with no unpleasant implications for doctors but some intelligent women find the term objectionable. The *cervical test*, or the *protection test*, may be useful alternatives and psychologically more acceptable.

Community Screening

Boyes *et al.* (1962) demonstrated this as a practical procedure and Fidler *et al.* (1963) examined 53% of women at risk in British Columbia by the end of 1962. Experienced technicians scanned 100 slides a day. In England and Wales it is estimated that the number of women at risk would be approximately 15 million and probably 5 million man-hours would be needed to complete the first examination—if all agreed to be tested! This is the equivalent of 70 trained staff working without ceasing 24 hours a day for 3 years, but the wider adoption of automation in processing and scanning will facilitate screening programmes. Difficulties are great but the rewards are greater. If results comparable to those already achieved in British Columbia were reproduced in Britain the number of new patients with cervical carcinoma would be reduced by at least 2,000 a year. The problem of obtaining the co-operation of the 50% at greatest risk, referred to earlier, challenges education, public health and medical authorities.

Davis (1962) devised an ingenious "do-it-yourself kit", consisting of a disposable plastic outfit in which a pipette containing irrigating and cell preservation fluid is enclosed in a light aluminium container.* It is the equivalent of a miniature douche and makes it

* This is supplied by Skandialab A/S, 16-18 Graabrodretor, Copenhagen, Denmark.

possible for women in isolated areas to send specimens by post. In one postal screening programme 85% participated and in the first survey carried out in Copenhagen 10,500 women were screened in this way. There was a diagnostic accuracy of 96% in a blind trial study involving 1,000 patients, 127 of whom had either Stage 0 or invasive cancer. The pipette has a lower failure rate than the spatula when there is a clinical carcinoma, an important point if facilities are not available for routine clinical examination.

Because of their importance the following points relating to cytology are re-emphasized:

1. *The cytologist does not diagnose cancer*

He reports the presence of malignant or suspicious-looking cells. They may indicate a malignant growth or a focus of dysplasia. Cancer is determined by what a cell does, not by what it looks like. The leopard in the cage may look vicious, and so may the epithelial cell with malignant characteristics, but as long as bars restrain the one and basement membrane the other, the dangers are potential rather than immediate.

2. *A negative test does not exclude cancer*

Cytological examination is only part of a careful clinical assessment as stressed by Younge (1957, 1965) and others. An unhealthy cervix should be seen by a gynæcologist *even if the cytologist's report is negative.* Garrett (1964) found false negatives in 13% of 30 early symptomless carcinomas. This is of clinical and medico-legal importance (Chapter 9), since cytology is now accepted in current clinical practice and its limitations must be realized.

Because of publicity in press, radio and television the demand for testing exceeds the available resources in some places. A gynæcological clinic can no longer be considered efficient if cytology is not included in the pelvic examination. Facilities in postnatal clinics could induce more women to attend for examination and help the screening programme.

Summary

Cervical cytology can be a means of selecting with considerable accuracy those patients who need further investigation. This is its objective, and no more than this can be expected from it. The better the smears the fewer the errors of interpretation. It detects lesions

invisible on clinical examination, and because of its limitations with an unhealthy cervix *biopsy is indicated irrespective of the cytological report* when inspection or palpation reveals an abnormality.

Results

Selection of material influences the incidence of Stage 0 and micro-invasive lesions and positive reports can be expected in approximately 5–10 per thousand of all patients attending gynæcological clinics. Younge (1958) found Stage 0 lesions in 12 per thousand. Howard *et al.* (1951) in 35 per thousand, and Boyes *et al.* (1962) in mass screening discovered 828 Stage 0 lesions in 146,833 women, a rate of approximately 6 per thousand. Anderson (1959) and Kellar (1958) detected 15 per thousand, including 3 micro-invasive growths in an Edinburgh general practice. The Oxford figure is 150 in 23,000 examinations or approximately 7 per thousand, and Garrett (1964) found 57 unsuspected lesions in 15,468 women attending a cancer detection clinic, an incidence of 4 per thousand.

Repeat Screening

When women report yearly for tests the rate of positive smears is relatively low. Smith (1957) recorded an incidence per thousand of 15 in 1954 and 7 in 1955 in the cytological service of the London Ontario Cancer Foundation, while Stern (1959) found an initial incidence of 6·7 per thousand, which fell to 1·2. In San Diego, Martin (1957) recorded a fall from 7·9 per thousand to 0·8. Garrett (1964) found 43 positive tests in the first year, 9 in the second, and only 5 in the following 8 years.

When suspicious cells are detected at the first examination and biopsy reveals carcinoma-*in-situ* it is not known how long the lesion has been present. It would be unsafe to presume that it would be years before invasion began. In the British Columbia survey not only has the incidence of invasive carcinoma per hundred thousand fallen from 28·4 to 15·5, but in 1961–62 only 12 of 193 new cases (6%) came from the screened population. This means that if the reduction in carcinoma of the cervix of 45% within 8 years is the result of detecting and treating Stage 0 lesions in only half the community invasion must have been imminent in many when Ca0 was first detected. While it is strictly correct to say that carcinoma-*in-situ* is not a killing disease, a description which is found in the literature, this is true only when it is established that micro-invasion

does not co-exist. Before this can be proved the Stage 0 lesion must be excised completely for histological examination. Moreover, when first detected the intra-epithelial lesion may be in the final stage of preparation prior to breaking through the basement membrane and becoming a marauding cancer. It follows therefore that from a practical, as opposed to academic, point of view to regard carcinoma-*in-situ* as not being a killing disease is comparable to giving a stiletto to a paranoic.

Colposcopy

Hinselmann (1925, 1938, 1951) devised the colposcope to make possible examination of the intensely illuminated cervix under high magnification. The cervix, cleaned with a dry swab, is painted with 30% acetic acid. This removes mucus and causes slight mucosal œdema which defines the features more clearly. Though used extensively as a diagnostic weapon in German and Austrian clinics its adoption in Britain and America has been slow. When a Zeiss colposcope was first used at Oxford a pinhead carcinoma was

FIG. 59. Portable Colposcope. Obtainable from Vann Bros. Ltd., 63 Weymouth Street, London, W.1.

detected in spite of negative cytology. Similar encouraging findings were reported by Bajardi and Burghardt (1957), Navratil (1957), Coppleson (1959, 1960) and Garrett (1964). Lesions can be photographed for record purposes and areas for biopsy can be localized, thus avoiding unnecessary cone biopsy. Readers interested in cervical changes seen through the colposcope are referred to the "Atlas Kolposkopie" by Mestwerdt.

Disadvantages are that the instrument is expensive (some models costing over £500 with camera attachment), requires experience for its use, and is unsuitable for screening because of time involved. Anderson (1962) devised an ingenious portable instrument (Fig. 59), marketed as the Vann-Watson Hand Colposcope at a basic cost of approximately £220, which can be used with the patient either in

Fig. 60a. Epithelial Dysplasia.
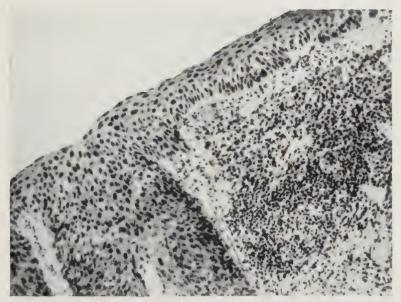
Fig. 60b. Carcinoma-in-situ.

lithotomy or lateral position. A camera attachment is available and sections of dysplasia and Ca0 detected with this instrument are seen in Figs. 60a and b. It should increase interest in colposcopy and prove valuable in precise diagnosis.

Colpomicroscopy

This is a refinement of colposcopy designed in Vienna by Antoine (1951) and Grunberger (1953, 1956). A cervix stained with hæmatoxylin can be examined with a magnification of 75–200 by direct light microscopy as described by Antoine *et al.* (1953) and Antoine and Grunberger (1956) in their *Atlas der Kolpomikroskopie*.

Enzyme Screening Test

When normal cells undergo dysplasia and progress to Stage 0 and invasive cancer, glycogen metabolism is disturbed. This is associated with chromatin and chromosome changes already described and with the increased nucleotide needs of proliferating cells. Bonham (1964) estimated the activity in vaginal and uterine fluid of 6-phosphogluconate dehydrogenase (6PGD). This is an

enzyme on the pentose phosphate pathway from glycogen to nucleotides which is active only in the presence of nicotinamide adenine dinucleotide phosphate ($NADP^+$), magnesium, and certain other ions. The method depends on the aspiration of vaginal fluid from the posterior fornix, its freeze drying to permit accurate weighing for assay, and the assessment of enzyme activity by estimating optical density with a spectrophotometer. Results are measured in units of 6PGD. In uteri with no epithelial abnormality there is either no activity or up to about 30 units. Figures of this order are more common in the presence of cervical polypi or secretory endometrium. The upper limit of normal was fixed by Bonham and Gibbs (1962) at 80 units.

An analysis was made of 700 assays on vaginal fluid from 380 patients of whom 105 had malignant disease. There was one false negative in a corpus adenocarcinoma. The false positive rate was 6% with infection a factor as in cytological testing. Positive tests were obtained from carcinoma of the vulva, secondary deposits in the vagina, sarcoma of the uterus and vagina, and from a melanoma. Ten patients with carcinoma-*in-situ* gave a range of 95–1,209 units, with an average of 653. Bonham advocated the test for screening and maintained that a relatively junior technician can be trained quickly to perform the assay. Other workers, while confirming the accuracy of the method with invasive carcinoma, in which the test is not necessary, were unable to reproduce effective results with Stage 0 lesions. Lawson (1965) stated that false positives occurred with infection, after the menopause, with vaginal bleeding and after operation. Sounding a note of caution he claimed that critical scepticism is necessary. The test is now on trial in London as a screening procedure.

Treatment of Patients with Stage 0 Carcinoma of Cervix

In theory this is simple, but in practice it can be difficult, hence the confusion which undoubtedly exists. Methods are employed as diverse as simple excision and radical surgery. Amputation of cervix, or cone biopsy are used in some clinics and irradiation in others. Reasons for this conflict include failure to appreciate the pathological significance of the lesion. A Stage 0 area may or may not be pre-malignant, and may or may not be associated with micro-invasion. Only time could settle the first question and biopsy the second, but if the diagnosis is correct it is *not* cancer in the clinically accepted sense of the word and does not invade, metastasize, nor recur. Radical treatment by either surgery or radiation is therefore not only unnecessary but contra-indicated. Accurate diagnosis is of

paramount importance but this is impossible unless the lesion is excised for histological examination. Even then mistakes can be made. Te Linde (1944) and Galvin and Te Linde (1949) found on re-examination of extirpated cervices that on 16 occasions when Stage 0 lesions were diagnosed it was possible by further examination to demonstrate micro-invasion in 15. This undoubtedly influenced the surgeons at the Johns Hopkins Hospital in performing radical surgery for pre-invasive cancer. Because Ca0 can be multifocal and associated with micro-invasion or clinical cancer, biopsy may reveal a completely excised lesion while leaving another focus. A postoperative smear would indicate the need for further investigation. A logical guide to practice based on these facts for all women with positive cytology would be as follows:

A. The Non-pregnant Woman

The clinically healthy cervix is examined with the Schiller test, by colposcopy, or by both methods. Suspicious areas are excised, but not with the diathermy knife which spoils the specimen for histological examination. If the excised area is small its base and edges are cauterized. If larger the incision is sutured with nylon. If the cervix is lacerated and a suspicious area is found in the tear this is excised in the postmenstrual phase so as to provide both a wide excision and the basis for an effective trachelorrhaphy. Interrupted figure-of-eight nylon sutures are tied just firmly enough to give hæmostasis and to avoid cutting into the cervix. They are left 2 cm. long to facilitate removal and the patient is discharged the next day. The stitches are removed in 3–4 weeks after the next period, and the smear is repeated. This technique reduces the risk of secondary hæmorrhage with breakdown of the repair so common when catgut is used. If the smear is negative clinical examination and tests are repeated in 3 months, 6 months, and then yearly. Pregnancy is not contra-indicated, but near the menopause hysterectomy with ovarian conservation is justified if anxiety is caused by the prospect and implication of repeated examination.

If the test remains positive after biopsy, or if no suspicious areas are detected at the initial examination, adequate cone biopsy is required. Nylon sutures are preferable to catgut for the reasons already given. Careful sectioning of the cone is essential to establish the correct diagnosis and complete removal of the lesion. If, following cone biopsy, the test remains positive (which seldom happens), it is the more important to re-examine the vaginal vault after applying iodine and to excise widely any unstained or poorly stained areas.

Younge (1965) found that in 500 patients with Stage 0 lesions the vaginal walls were involved in 2%. If the vault is healthy, hysterectomy by either the abdominal or vaginal route is indicated. The decision to advise this is obviously the more difficult the younger the patient, and the smaller her family. It should be appreciated by all concerned, including the patient and her husband, that postoperative examination of the uterus might not disclose any abnormality in spite of the positive cytology, but on the other hand, it might reveal micro-invasion. For this reason there is justification, particularly near the menopause, for one pre-operative application of radium into the cervical canal. Ellis (1963) stated that a single dose of 400 r will reduce the number of fertile cancer cells to 6%. An application of 50 mg. for 24 hours will not interfere with postoperative healing and will reduce the danger of implantation or dissemination of malignant cells should an unsuspected cancer be found in the extirpated uterus. The problem is difficult, the implications are serious, and it is a wise precaution to have adequate documentation of what was advised and why (Chapter 9).

Fortunately is most cases the methods suggested will remove Stage 0 lesions without the need for hysterectomy, and subsequent tests will remain negative. The ease with which an area of carcinoma-*in-situ* can be removed even by swabbing was emphasized by Haines (1965). An unanswered important question concerns the increased risk, if any, of a woman developing further Stage 0 lesions when one is removed. It is reasonable to assume that once there has been epithelial dysplasia the risk of it recurring is increased, but this is not necessarily correct. Frequent screening of these patients is advisable and should be at least once a year. The Royal College of Obstetricians and Gynæcologists is conducting an extended survey on carcinoma-*in-situ* which might provide answers to some of these questions.

B. *The Pregnant Woman*

Ca0 associated with pregnancy is even more difficult. There are more errors in interpreting slides from pregnant women, and when the test is positive the question of biopsy and conization has to be considered with due regard to the increased risks involved. In some clinics it is felt wiser to concentrate available facilities on screening the non-pregnant population in the first instance, while endeavouring to arrange for postnatal tests 6-8 weeks after delivery. When the test is positive it is essential to re-examine the cervix clinically with good illumination, and the Schiller test and colposcopy are helpful.

If no lesion is demonstrated the possible alternatives are either to wait until the puerperium, and if the test is still positive to perform conization or biopsy, or to take a cervical biopsy during pregnancy. We do not advise this because of the danger of hæmorrhage and abortion, but without it there is the small danger of micro-invasion progressing to clinical cancer. This risk must be weighed against the danger of the procedure.

The incidence of cervical cancer in pregnancy is approximately 1 in 5,000, whereas Stage 0 lesions could be expected in at least 15–20, and dysplasia sufficient to produce suspicious cells in a corresponding number. This would mean subjecting the cervix of 30–40 pregnant women to biopsy for every carcinoma of the cervix detected and the risks would not justify this. Baker *et al.* (1961) reported 2 abortions and 1 premature labour following conization in 16 pregnant women, but in spite of this considered biopsy justified. Boyd (1958) reported postoperative hæmorrhage in 13 out of 80 patients on whom conization was performed. Ten required transfusion and one hysterectomy was necessary after the administration of 5 l. of blood. This is a high price to pay. McLaren (1964) advises a more conservative approach and adopts no hard and fast rule. He considers each patient as a separate problem with a possible bias towards allowing the mother to carry the very small risk of undetected invasion in the interests of her infant's survival. To reduce the risk to its minimum he employs inspection of the cervix under anæsthesia, colposcopy, and punch biopsy instead of conization. If malignant-looking cells are found in repeated tests there is a stronger indication for biopsy or conization than if the cells are merely suspicious. Nylon sutures lessen the danger of hæmorrhage after conization.

Carcinoma of the Cervix
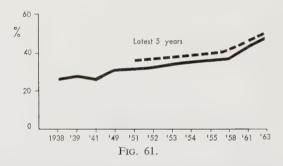
Emphasis is now on the detection of Stage 0 lesions and the prevention of cervical carcinoma, but for a long time there will be women with this disease. It will be diagnosed in its early stages in increasing numbers and there is urgent need for re-appraisal of existing therapeutic procedures. It is *not* wishful thinking to plan and work for the day when at least 70–80% of all patients with uterine cancer will be cured.

Presenting a report on 325,000 cancer patients at the American National Cancer Conference (1964), the National Cancer Institute Statistician concluded that surgery and irradiation had exhausted their potential for further improvement, but the President of the

Cancer Society took a contrary view and stated that it was necessary to explore "other combinations of these two most effective therapeutic weapons". Increasing realization of the need for team work by radiotherapists and surgeons in exploring the potential of existing techniques, and the development of new ones, is an important advance.

In 25 years since 1938, the 5-year prognosis for patients with cervical cancer improved by 84% from 26·3% to 48·6% (Fig. 61). The latest 5-year results are represented by the dotted line. These figures are collected from a considerable material, 117,613 patients from 1948–57. In many institutions the prognosis is much better

FIG. 61.

than indicated by the graph, as in Radiumhemmet, Stockholm, where in 1953–57 it was 54·5%, in Zurich 64·6% and the Royal Victoria Hospital, Montreal, 70%. In other clinics the results are worse, but sources of error include random fluctuations as high as 12%. If reasons for the variations could be defined, and avoidable factors detected, there would be less danger of complacency in regard to the improved results now generally achieved. In view of the wealth of clinical and pathological material it is surprising that so many questions remain unanswered. A brief historical summary reveals changing trends in thought and practice, and the reasons for them.

Historical Summary

The pioneer work of Clark (1895, 1896, 1906), Ries (1906, 1913), and Wertheim (1905) established that cervical cancer spreads through parametrium and paracolpos to the pelvic walls and glands.

Their surgical techniques, based on this knowledge, aimed at extirpating these areas. Surgery had a high mortality and morbidity but offered the only available prospect of cure at that time. With the use of radium early in the twentieth century a new era dawned. Two facts became apparent, the primary growth did not always respond and even when it did some patients died later from pelvic metastases. Radium treatment, unlike surgery, could be used irrespective of the age of patient, general health, or stage of growth and even when this was advanced there were occasional successes. Gynæcologists with 100 or more mg. of radium achieved a 5-year cure rate of approximately 20%, but when radiotherapy departments developed, many women with genital cancer were treated without being seen by a gynæcologist. Recent progress in radiation techniques has brought closer liaison between physicians, surgeons and radiotherapists.

Meanwhile, surgical techniques and facilities have improved. Sepsis control, better anæsthesia, blood transfusion, and a better understanding of biochemistry have contributed to success. In Japan surgical treatment is preferred to irradiation and has a better prognosis for all stages (Table 43). The surgical results reported by Magara (1963) for the years 1953–54 are not only much better for all stages of growth than the corresponding figures in a series of comparable size treated by irradiation in Japan, but they appear at first sight to be better than the results reported from Stockholm by Kottmeier for the years 1950–54. They are apparently much better than the results obtained in the huge collected series of 49,235 patients (1950–54) reported in the Annual Report on the Results of

Table 43

RESULTS OF TREATMENT. (Magara)

1953 - 54

Stage	Number Operated on	5 Year Cure %	Number Radiated	5 Year Cure %
1	762	83.1	136	55.2
2	1165	62.0	464	42.7
3	418	44.8	916	24.9
4	14	7.1	378	9.8
1 - 4	2359	65.4	1894	28.5

Treatment in *Carcinoma of the Uterus*, Volume 12, but the series are not really comparable. The Japanese surgical results were achieved in treating 2,359 patients selected from a total of 4,253 with cervical cancer. The relative percentage of 5 year cures for all patients treated in the Japanese series were 65·4 by surgery, 28·5 by irradiation and 49 for the total group. The latter figure is the only one which could be compared with Kottmeier's results (Table 44) or those of the international collected series. It is not as good as the former but better than the latter. Considerable variations exist in results obtained either by radiation or surgery on growths of comparable staging, and

Table 44

RESULTS OF TREATMENT. (Kottmeier)
1950 - '54.

STAGE	Collected series 5 Year Cures	Radiumhemmet 5 Year Cures
1	73.2%	89.0%
2	51.2%	59.5%
3	26.7%	34.5%
4	7.3%	6.3%
Patients: 49,235	46%	1,933 (55.6%)

if the reasons for this can be discovered there is more hope of general improvement. Analysis of the records of cured patients is encouraging but a study of those who die can be more instructive, as demonstrated by Henriksen (1949). Correlated with research on the living it can answer some unanswered questions.

Methods of treatment have been retained longer than was justified by their results. If a tumour spreads to adjacent structures and metastasizes to pelvic glands, the only logical treatment would be one capable of destroying cancer cells in all these sites. Philosophically speaking, the problem of treatment is as simple as that. As it will seldom be known until too late that invasion is widespread every patient should theoretically be treated on the assumption that it is. This may be impossible in practice, or achieved only at the risk of complications so serious that it would not be justified. For these reasons inadequate methods were sometimes adopted and retained when therapeutic advances removed the original

justification for their use. Abdominal surgery designed to extirpate the whole area at risk carried a high primary mortality when first introduced, and the Schauta vaginal technique became popular. Ignoring the glands, it permitted a wide excision of the remaining potentially malignant tissues and reduced the operative mortality. It accepted the implication that at least 20–30 % of patients would retain malignant pelvic nodes from which they would die, if they survived the initial operation. In many clinics the technique was not adopted for this reason, but the combination of lymphadenectomy with the Schauta (1904) technique was a logical advance. Mitra (1959) confirmed in practice the theoretical justification for the extended operation. He found glands in 25 % of patients (Stage 1— 18 %, Stage 2—29 %, Stage 3—40 %) and raised his 5-year cure rate from 44·5 % to 61 %. More recently the excellent figure of 78·7 % was reported by Navratil (1965) for the 5 year cure rate in 276 patients with stage 1 carcinoma, 120 with stage 2 and 3 with stage 3. The fact that these results were achieved without treating the glands is a tribute to the author's skill and experience. What improvement would follow in the Austrian series if the vaginal operation were combined with irradiation of the pelvis or with lymphadenectomy as in Mitra's series has still to be demonstrated. Moreover these days it is becoming progressively important when considering stage 1 carcinoma to know the incidence of stage 1a, for which excellent results can be obtained and in which the incidence of gland metastases is likely to be extremely low. This is a subject on which more information is required.

Irradiation for cervical cancer commenced with a local attack by radium, which cured some patients but was doomed to failure when glands were involved. There has been reluctance to recognize the high incidence of node metastases, and the doubtful therapeutic effect on these of uterine and vaginal radium and deep X-ray therapy. Parsons *et al.* (1960) found node involvement in 38 % of 103 patients who failed to respond to irradiation. Recent advances in megavoltage therapy are encouraging, but the incidence of malignant glands is crucial and vitally concerns any method of treatment, or combination of methods. Parsons found an incidence of 19 % in another series of 104 patients and compared this with the 16 % incidence reported from the Mayo Clinic in 167 patients, of whom 155 had early Stage 1 growths with glands in 12·2 %. Graham (1955) reported node deposits in 15 % of Stage 1, 27 % of Stage 2, and 66 % of Stage 3 growths, while Bonney (1941) found glands in 40 % of 500 patients. Navratil (1954) in 1,010 patients found an incidence of 11 % in Stage 1, 23 % in Stage 2, and 43 % in Stage 3.

On the other hand, *Lange* (1960) *found node metastases in* 28·8% *of* 146 *patients with Stage* 1 *carcinoma and in* 43·8% *of* 32 *with Stage* 2. He attributed these high figures to the meticulous care with which glands were examined and in 40% only microscopic metastases were demonstrated.

Rutledge *et al.* (1958) studied the effect of radiation on glands. They cut two sections from each gland removed from 100 patients, and serial sections of glands from 20. Cancer was found only once by the serial technique when not revealed by the two-section method. They concluded that serial sections are unnecessary, but there are possible fallacies in this deduction. Lange's positive demonstration of malignant cells is more relevant than failure to detect them in the smaller American series. Furthermore, in the Scandinavian study preoperative irradiation had not been given, whereas in the American series it had, and the glands most likely to respond would be those with small or microscopic deposits. Even so, when operation was performed on 34 patients who failed to respond to irradiation, positive glands were found by Lange in 16 (47%).

This evidence, selected as representative from an extensive literature, establishes the following points relevant to treatment and prognosis:

1. Gland metastases can occur early and have an average incidence of 16·5% in Stage 1 growths, increasing as the cancer spreads until it is 46% or more in Stage 4.
2. Large glands can be detected by vaginal or rectal examination. Those not palpable may be demonstrated by lymphography, (Liebner *et al.*, 1964), but the pathologist may demonstrate histological cancer even when there is no palpable evidence of metastases at lymphadenectomy.

Palpable nodes may or may not be malignant. Antoine (1951) found that only 17 of 30 malignant nodes were suspected at operation, identical figures to those reported by Grünberger (1953). Glucksmann *et al.* (1953) found that 58% of enlarged nodes were malignant, and unsuspected cancer was found in 24% which were not palpable. Tachibana (1956) and others reported similar findings. The larger, harder, more irregular, and fixed the glands are the greater the chance that they are malignant, but *almost* 50% *of malignant nodes are not palpable*.

Selective lymphadenectomy, which began with Gellhorn (1905), removes isolated palpable glands. This unsatisfactory procedure was introduced to reduce the high mortality and considerable

morbidity then associated with bilateral lymphadenectomy. There is no longer justification for techniques which are basically inadequate. Glands require treatment, but the issue is controversial whether this should be by surgery or irradiation designed to deal with the whole area at risk. This means systematic dissection, or irradiation of the pelvic lymphatic area, or a combination of both methods. In many clinics glands are not treated because emphasis has been on treating the primary growth as advised by Parsons *et al.* (1960). At one time there were powerful arguments to support this attitude, for unless the primary cancer is cured the patient dies a miserable death, but if the cervix heals and there are no metastases she survives. When metastases are present the prognosis depends on the efficacy of techniques available for treating them, and conventional radiation methods offer little encouragement. Megavoltage therapy, improved surgical techniques, and combinations of both have improved the prognosis and introduced a new era in cancer history.

Unnecessary surgery or irradiation, both involving risks, could be avoided if it were possible to select those patients without metastases, but unfortunately it is not. Radiosensitivity assessment as described by the Grahams (1953), Glucksmann *et al.* (1945, 1948), Davis *et al.* (1960) and others may even confuse the issue. Paradoxically its accuracy constitutes its main source of error because radiosensitivity and radiocurability are not synonymous. A radiosensitive tumour may be expected to respond to effective irradiation, and by so doing confirm the opinion of the cytologist as reported by Glucksmann *et al.* (1964), but the prognosis will be poor if there are metastases which are either not treated or are dealt with inadequately. Whether death is due to primary growth or metastases is a point of academic interest, but appraisal of the mode of death can be important in influencing therapeutic trends. Search for avoidable factors in these deaths is likely to accelerate progress.

A logical practical approach is that either the whole area at maximum risk must be treated in every case, or an effort be made to select those patients with the greatest risk of developing metastases. There is evidence that gland involvement may be influenced by the following factors:

(*a*) Size of primary tumour.
(*b*) Differentiation of tumour cells.
(*c*) Stromal changes.
(*d*) Associated pregnancy.

Size of Tumour

As cervical cancer extends from Stage 1 to Stage 4 the incidence of metastases progressively increases but even in Stage 1 its size is important for two reasons. The larger it is the more refractory it becomes to irradiation, as described by Fletcher *et al.* (1962) and Ellis (1963), and the greater the incidence of metastases. Lange (1960) found that nodes were involved in 11% of patients when the primary ulcer was less than 1 cm. in diameter, in 26·5% when the diameter was 1–3 cm., and to 47·1% if greater than 3 cm. The glands most often involved were the hypogastric and obturator. Endocervical tumours metastasize more frequently than others. These facts help to explain why large endocervical growths do not usually respond well to irradiation.

Differentiation of Tumour Cells

Well differentiated tumours rarely metastasize (Lange, 1960). Stallworthy (1964) found anaplastic tumours in 70% of patients with positive glands. Gusberg *et al.* (1953), Cherry and Glucksmann (1955), Botella Llusia *et al.* (1962), all emphasize the correlation of anaplasia and lymphatic emboli, which also applies to corpus carcinoma. Not all authorities accept the classification of Broders (1922), Martzloff (1928), Glucksmann (1956) or others, and the grading of cells in a biopsy specimen is not always supported by the study of the whole tumour. There is usually little disagreement over well-differentiated and anaplastic cells, but differences of opinion can arise over intermediate grades. This does not invalidate the fact that *the more poorly differentiated the tumour the greater the risk of metastatic spread.*

Stromal Changes

A connective tissue reaction to invading cancer cells has been studied extensively by German workers since Schottlaender and Kermauner (1912) described three types: medullary tumours with little connective tissue, scirrhous tumours with much connective tissue, and mixed patterns. They also described an inflammatory type of cellular infiltration with eosinophilia in 36% of patients, a figure almost identical to that reported by Fluhmann (1927). Bruntsch (1956) maintained that a high degree of eosinophilia was associated with increased lymphatic invasion and Lange (1960) concluded that a scirrhous response increased the risk of gland deposits. If these observations are confirmed they illustrate the

importance of a detailed report on a biopsy specimen. "Squamous cell carcinoma", if correct, confirms the diagnosis, but a description of the tumour cells and the stromal reaction could be a guide to treatment when this is individually specialized as advocated by Gray and Kottmeier (1957).

Associated Pregnancy

Evidence that glands are more frequently involved in pregnancy is suggestive rather than conclusive. No centre has a great experience of these patients, the material analysed in the literature is not large, and factors such as those outlined above have not been taken into critical consideration. Fletcher *et al.* (1962) stated that in a small series of pregnant women with carcinoma of cervix, lymphadenectomy revealed a higher incidence of positive glands than in non-pregnant patients. Fluhmann (1961) believes that pregnancy makes no difference.

The four factors described above, either alone or in combination, indicate an increased possibility of lymphatic invasion, but the carcinoma may remain localized in spite of them, or in their absence may metastasize. It follows therefore that *ideally the area at risk should be treated in every case*.

An important corollary is that the effect on prognosis of treating these areas will depend on three things:

1. The incidence of metastatic cancer.
2. The dangers involved.
3. The efficacy of the treatment.

The incidence of gland deposits ranging from 10% to 50% has been reviewed earlier. When the lowest mortality of surgical treatment was $10–20\%$ and the prospect of 5-year cure after operation was only $30–40\%$ (Wertheim, 1905; Bonney, 1941), techniques adequate for the primary tumour, but not for peripheral spread, improved the overall prognosis by lowering the primary mortality. The Schauta technique was an example. Those days have gone and with them the justification for procedures which leave untreated potentially malignant areas in at least $20–30\%$ of which cancer cells remain to kill the patient. Teams skilled in the relevant anæsthetic and operative techniques can now extirpate the areas at risk with a mortality of less than 1% as shown by Meigs (1949, 1955, 1956a and b). Magara (1963), Currie (1963), Stallworthy (1960, 1964) and many others, but this does not justify surgery if similar or better results are possible by alternative techniques with less morbidity. Whether this stage has yet been reached can be decided only after reappraisal

of what these other methods can achieve. For practical purposes they are radiotherapy, alone or in combination with surgery, cytotoxic drugs, or hormones.

Radiotherapy

Uterine and vaginal radium has an effect, though limited, on gland metastases. Kottmeier (1951) measured the amount of radiation received by glands using the Stockholm technique of radium application and detected variations from patient to patient according to the position of the glands and the condition of the vagina. With a mobile distensible vagina, obturator nodes received approximately 2,000 r and hypogastric and external iliac 1,000 r. The dose decreased with a short or stenosed vagina. He claimed that irradiation could sterilize glands, but in 1955 stated that regional nodes "can be destroyed in some cases". These views received support from Rutledge and Fletcher (1958), Botella Llusia *et al.* (1962) and Glucksmann *et al.* (1964), but the latter found in radio-sensitivity studies that some patients whose primary tumours disappeared died from node metastases. They therefore performed lymphadenectomy on alternate favourably responding patients 8 weeks after completion of radium treatment. Analysis of 10-year results with Stage 1 cancer revealed that radium cured 62% and radium plus lymphadenectomy 83%. The corresponding figures with Stage 2 were 35% and 52%. The same trend was demonstrated in 419 patients irrespective of whether the tumour was radiosensitive or not, suggesting that surgery improved the prognosis. That irradiation can destroy gland metastases is an important observation, but before considering it a reliable therapeutic weapon for the purpose it is necessary to know how often this occurs, what doses are required, and how they are best administered. Although a final answer is not available to any of these questions valuable information is accumulating.

The effect of megavoltage techniques on pelvic glands has been tested. Fletcher *et al.* (1962) using a 22 mev betatron delivered 4,000 r to the whole pelvis in patients with Stage 1 and 2 cancer and concluded that:

1. This technique is simpler than radium and deep X-ray therapy and obviates the need for individual detailed attention.
2. Results are improved with a 5-year apparent cure rate of over 60% for all patients treated:
   Stage 1, 90%; Stage 2, 75%; Stage 3, 40%.
3. It does not preclude surgical intervention.
4. It sterilizes glands in some cases.

Evidence on this last point was obtained from 430 post-irradiation lymphadenectomies. Positive nodes were found in 2·5% of 41 patients with Stage 1 cancer, in 13% of 123 with Stage 2, and in 19% of 170 with Stage 3, as compared with 15% in Stage 1, 27% in Stage 2, and 66% in Stage 3, when direct irradiation was not given to the pelvic walls (Graham, 1955). The incidence of positive nodes before and after irradiation is given in Table 45.

Gorton (1953) reduced the incidence from 30% to 13·6% by deep X-ray therapy. Botella Llusia *et al.* (1962) after 5,000–7,000 r to the pelvis reduced node metastases from 33% to 6·7%, but as the material was small these figures should be accepted with reservation. Morton

Table 45

EFFECT OF RADIATION THERAPY ON GLANDS.

			TECHNIQUE	% WITH GLANDS	
BONNEY	1941	No	Irradiation		40
GORTON	1953	No	Irradiation		30
GORTON	1953	Yes	Radium & X-Ray		13.6
SWEENEY & DOUGLAS	1962	Yes	Radium & X-Ray		16.7
CURRIE	1963	Yes	Radium 1 application		30
MAGARA	1964	No	Irradiation		37.7
MORTON	1964	No	Irradiation		23.7
MORTON	1964	Yes	Radium & Mega-voltage		12.5
STALLWORTHY'64		Yes	Radium 3 applications		22

0   50   100

et al. (1964) investigated 70 patients with Stage 1 cancer on 38 of whom a primary lymphadenectomy was performed before radiation was given. The remaining 32 had irradiation followed by lymphadenectomy and the same team conducted the whole investigation. The number of glands removed varied from 13 to 22. Enlarged ones were not always malignant, nor were normal-sized ones always free of cancer. Radium was applied to the cervix, combined with mega-voltage therapy to the parametrium and node-bearing area using

Cobalt 60 or cæsium. Approximate doses were 8,000 r at point A, 4,500 r at point B, and 12,000–20,000 r to the cervical canal. Lymph node metastases were found in 23·7% without irradiation and in 12·5% after it. Postoperative complications were minor. Rutledge and Fletcher (1958) gave 6,000 r to the whole pelvis in 6 weeks with a 22 mev betatron in a series of 100 consecutive patients with Stage 3 tumours and followed this by lymphadenectomy. Positive glands were found in 14%, a figure similar to the 19% reported by Fletcher *et al.* (1962) after 4,000 r. The expected incidence without irradiation was 46–66%.

Summary

These studies demonstrate the following points:

1. There is a high incidence of node metastases in cervical carcinoma irrespective of the stage of primary growth.
2. The incidence is reduced even after radium treatment.
3. When this is combined with irradiation of the gland fields by conventional deep X-ray therapy there is a greater reduction.
4. The incidence is lowest after megavoltage therapy.

The available evidence supports the view expressed by Sweeney and Douglas (1962) that there is as yet no method of destroying by irradiation all lymph node metastases, but their estimate that residual malignant cells could be expected in 10–14% of Stage 1 tumours, 16–20% of Stage 2, and 25–35% of Stage 3 after megavoltage therapy is probably too high.

Lymphadenectomy is essential when carcinoma of the cervix is treated surgically by either the vaginal or the abdominal route, but the facts reviewed above establish a logical basis for its use following irradiation, although before a technique can be recommended the results it can achieve should be weighed against the risks involved.

There has been an unjustified defeatist attitude over gland metastases. Bonney (1941) and Taussig (1943) reported 5-year cures in 21%. Taussig's first patient treated in 1930 had one malignant hypogastric gland and was alive and well 13 years later. Mitani *et al.* (1962) claimed a good prognosis with a single large node, and 22 out of 33 patients in this category were well 5 years later. Sweeney and Douglas (1962) reported a 5-year apparent cure of 29% when irradiated malignant glands were removed, and Stallworthy (1964) a comparable figure of 27% after the application of radium to only the primary growth. He believed better results would follow pre-

operative irradiation to gland fields. Currie (1963) had the remarkable 5-year survival of 34 out of 69 patients (50%) with malignant nodes when high energy irradiation was given postoperatively. Kelso (1959) reported almost identical results with 50% 5-year survival in patients with Stage 1 and Stage 2 tumours and positive glands; (Stage 1, 66·6%, Stage 2, 43·1%). Morton (1964) found an average of 39·8% in the figures published by eight surgeons. Kottmeier (1965) stated that it is now not surgery versus radiation, but which technique should be used and when, an attitude which marked an important change from the traditional Radiumhemmet approach. The collected evidence confirms that lymphadenectomy has been followed by 5-year cure in 20–50% of patients with malignant glands, and these results can probably be improved. They must be weighed against the surgical risks involved.

Bonney (1941) found that adherent malignant glands increased the technical difficulties of operating, and the mortality and morbidity. His mortality was 14% for Wertheim hysterectomy and should not be compared with modern results either for the same operation or for lymphadenectomy performed after irradiation or vaginal surgery. Anæsthetic, biochemical, and surgical advances have produced great changes since Bonney pioneered this field of radical surgery, and the same procedures are now performed with much greater safety. Currie (1963) reported a primary mortality of 1·25% in 400 Wertheim hysterectomies performed since 1935, Magara (1963) 0·46% in 214 operations between 1955–62, and Stallworthy (1964) 0·7% in 285 post-irradiation Wertheim hysterectomies between 1950–63. Lymphadenectomy performed after irradiation, but without hysterectomy, as reported by Taussig (1943), Rutledge (1958) and Morton (1964) had a mortality of 0–1%. Taussig suggested that surgeons untrained in radical surgery could improve the prognosis for their patients by performing lymphadenectomy after irradiation. His operative mortality for 175 patients was 1·7%, later reduced to 0·7%. He excised the external iliac vein five times and the artery once, with no permanent ill effect, when glands were adherent. Stallworthy (1964) described the hard irregular gland fixed to vessels as being in a pseudo-capsule and by delicate sharp dissection a plane of cleavage can be defined, enabling the tumour to be removed with preservation of the vessel.

Three complications of lymphadenectomy are:

1. Postoperative œdema.
2. Ureteric fistulæ.
3. Lymphocysts.

Postoperative Œdema. This is common after lymphadenectomy whether performed with hysterectomy or as a solitary procedure. It can be unilateral or bilateral. Rutledge and Fletcher (1958) in a series of 100 lymphadenectomies found that most patients developed postoperative œdema of the lower limbs which generally disappeared within 6–8 months. It may occur suddenly, or insidiously weeks after operation, and prompt treatment improves the prognosis. The shorter the time the limb remains swollen the better the prospect of ultimate cure. A short initial period of resting with the feet elevated, massage, and diuretics produce rapid improvement. Supporting stockings should be applied while the limb is of normal size in the morning before rising. Short intervals of rest during the day with the feet elevated are indicated if recurrent swelling develops.

Ureteric Fistulæ. The risk to the ureter is much less when lymphadenectomy is performed as a solitary procedure than when it is associated with extended hysterectomy. Operative difficulties and risks are increased when malignant glands are fixed to the pelvic wall and vessels. Bonney's Wertheim mortality was 20% with malignant glands, and 10% when nodes were free of cancer. If the ureter is displaced medially as a preliminary step in lymphadenectomy it need not be damaged either at operation or subsequently by necrosis. It is rarely invaded by cancer but if this happens the affected segment is resected and the proximal ureter is implanted into the bladder. The risk of fistulæ following lymphadenectomy should be negligible.

Lymphocyst (Lymphocele) This is a cystic collection of lymph-like fluid on the pelvic wall or in the iliac fossa, to which little attention has been given in the literature. Rutledge and Fletcher (1958) reported a 31% incidence following 100 consecutive lymphadenectomies, with 21% bilateral and 10% unilateral. Gray *et al.* (1958), finding a minimum incidence of 16% following lymphadenectomy, believed that irradiation increased the risk and abandoned the combined procedure. Mori (1955) had an incidence of 47% after primary radical hysterectomy and 58% when preoperative irradiation was used. Following 140 operations there were 68 patients with lymphocysts. McDonough (1958) reviewing the literature found the incidence varied from 15% to 50%. He believed that the risk increased with the number of malignant glands removed. The more difficult the operation and the more experienced the surgeon, the greater the danger, probably because a more thorough dissection of the gland-bearing area is made.

Rutledge *et al.* (1959) studied a series of 281 lymphadenectomy patients. Preoperative irradiation had been given to 266, and in 81 lymphadenectomy was combined with hysterectomy. Lymphocysts developed in 68 patients (24%); in 18% with Stage 1 cancer and in 32% and 30% with Stages 2 and 3. Postoperative drainage with aspiration did not prevent the development of these cysts. Pressure on the bladder and bowel sometimes caused dysuria and consti- pation. Lower abdominal pain when walking was another complaint. Trypsin 5 mg. daily intramuscularly had no obvious effect on inci- dence but cysts were possibly smaller. Œdema of the lower limbs practically always disappeared within 9 months and supporting stockings were seldom required. After 100 consecutive lymph- adenectomies on patients with Stage 3 carcinoma, Rutledge and Fletcher (1958) found 31 developed lymphocysts which were large in three. Ten developed within 4 weeks of operation, 12 in the second month, 5 in the third, and 4 later than this, but during the first postoperative year. Bonney made no mention of lymphocysts. This may be partly because his primary mortality was 20% in just those patients most likely to develop lymphocysts, namely those with fixed malignant glands.

There are two types of cyst. One, detected within 2 or 3 weeks of operation, is a soft pelvic tumour lying between bladder and rectum like a thin-walled ovarian cyst of restricted mobility. If large it may be palpated in an iliac fossa and pelvic pressure symptoms may occur. It is too soft and flaccid to be a hæmatoma and there is no clinical evidence of concealed hæmorrhage. Aspiration drains a fluid resembling urine, but it is opalescent, contains no urea, is sterile, and has a high cholesterol content with some lymphocytes. Repeated aspiration may be needed before the cyst resolves. The more common type is palpated in the iliac fossa at the postoperative examination, usually 6–8 weeks after operation. It is smooth, hard, fixed to the pelvic brim, not tender, and may be too high and too small to feel rectally. A common mistake is to regard it as a recurrent malignant mass, and the longer the interval since operation the greater the chance of error. This has probably been one reason why lymphocysts have been diagnosed so seldom. In case of doubt an extraperitoneal incision reveals a smooth egg-shaped swelling adherent to the pelvic brim. Aspiration produces an opalescent fluid but the fibrinous capsule may be hard and so thick that it does not collapse. For this reason we have deliberately opened cysts into the peritoneal cavity so that peritoneum would replace the lining membrane and the masses have resolved without further difficulty.

The cyst usually resolves slowly, sometimes taking more than a year in the process, but surgery is unnecessary.

Treatment of Primary Cervical Cancer

The steadily improving prognosis (Fig. 61) reflects progress chiefly in radiotherapy, because this is the treatment most widely used. The latest 5-year cure rate is $48 \cdot 6\%$ (International Report, Volume 13). Even so, more than 50% of women die from the disease within 5 years of treatment and in many clinics the figure is nearer $60-65\%$. The earlier the stage of invasion the better the prognosis, whether treatment is by radiation or surgery, as illustrated by the excellent results achieved with micro-invasive tumours (Stage 1a). The 5-year prognosis for all patients registering with carcinoma of the cervix at the Royal Victoria Hospital, Montreal, is now 70%, because of the number with micro-invasive lesions (Latour, personal communication).

Kurrle (1960), Sweeney and Douglas (1962), and Stallworthy (1964) investigated changes in the uterus, parametrium and glands following irradiation. Their findings (Table 46) are remarkably similar and demonstrate a high incidence of residual malignant cells. According to Rutledge and Fletcher (1958) it takes 2–3 months for cancer cells to disappear or disintegrate sufficiently to be no longer viable, but they also had 22% of patients with glands containing active looking cells following megavoltage irradiation and intra-uterine radium. As serial sections were not made in any of the above series the true incidence of residual malignant foci could well be higher. It can be

Table 46

RESIDUAL MALIGNANT CELLS FOLLOWING RADIATION THERAPY.

		No.of Patients	Radiation Technique	% Incidence of Malignant Foci		
				Uterus	Para-metrium	Glands
KURRLE	1960	235	Radon + Deep X-Ray	30	–	21
KURRLE	1960	7	Megavoltage	14	–	0
SWEENEY & DOUGLAS 1962		102	Radium + Deep X-Ray	36	1	16
STALLWORTHY 1964		223	Radium	43	8	22
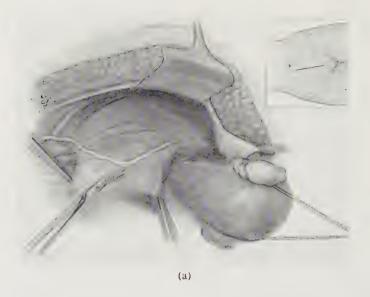
NB. The Parametrium was not reported on in Kurrle's series.

impossible to recognize viability by histological examination, but only 35% of the 567 irradiated patients in the collected series (Table 46) had residual cells in the uterus, which means that in 65% the tumour disappeared completely within 6 weeks of treatment. It is probable therefore that the figure of 35% gives a reasonable indication of the incidence of primary cervical cancers persisting after irradiation.

In 1940 the 5-year cure rate in the International Report was 26% and at Oxford 22% after radium therapy. A few experienced surgeons achieved a 5-year survival of approximately 40% on selected patients, but there were few such masters. An operability rate of 60% was considered high, mortality was 10% and more, and morbidity was considerable with a fistula incidence ranging from 1% to over 10%. It seemed significant that 143 (74%) of 193 recurrences following Bonney's first 500 Wertheim hysterectomies occurred in the operation field, although precautions were taken to limit the dissemination of malignant cells. The surgery of bladder, bowel, and other organs confirmed that viable cells spilled at operation could grow in incisions of approach, and there was also the possibility of blood and lymphatic dissemination. These facts suggested that preoperative radiotherapy might offer advantages over either technique used alone. It seemed logical that if a cancer were irradiated by lethal tumour doses prior to operation the risk of implanting or disseminating cells would be reduced. Furthermore, if the area at risk could be removed there would be no local recurrence. Although it was not known at the time, Schlink (1960) had already begun using preoperative irradiation before these views were tested clinically at Oxford in 1939. Important problems to be solved were the optimum interval between irradiation and surgery, whether operative difficulties and dangers would be increased, and whether improved prognosis would justify the procedure. Bonney (1930) agreed with Heyman that surgical interference "could affect adversely the good effect of radiation", and he and other senior colleagues with whom these views were discussed believed the dangers were considerable of operating after irradiation.

The first patients for combined treatment were selected carefully. They were in good general health and had Stage 1 cancers. Three radium applications by the Stockholm technique gave a total exposure of 7,200 mg./hours with an estimated dose of approximately 6,000 r at point A. The decision to operate 6 weeks after the first application proved fortunate. Way (Glucksmann *et al.*, 1964) operated on 7 patients within a week of the application of radium

(a)

(b)
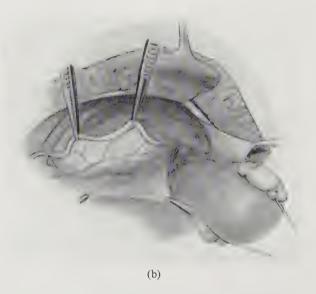
FIG. 62. a Ureter on posterior layer of broad ligament.
b Ureteric mesentery with vessels.

when reaction was at its height and they "did very badly". Bonney's surgical technique was used, including spinal anæsthesia, with two modifications designed to protect the ureter and uretero-vesical junction, areas at risk from delayed necrosis even without preliminary irradiation. Novak (1963) reported an incidence of $11\cdot4\%$ ureteric fistulæ in 246 Wertheim operations performed from 1947–53, but reduced this to $2\cdot8\%$ in 850 operations from 1950–62 with a technique designed to protect the terminal ureter.

The pelvic ureter lies in a loose areolar tissue tunnel as it crosses the posterior layer of the broad ligament. Vessels run longitudinally on its surface and are supplemented by a fine plexus *ascending* from the pelvic floor. An incision made above and parallel to the ureter allows it to be dislocated downwards to permit of division of the parametrium and paracolpos while preserving a delicate mesentery containing the anastomosing vessels. When there is chronic pelvic infection or endometriosis it is sometimes impossible to retain this mesentery intact, but even so the vessels can be displaced without being cut (Fig. 62*a* and *b*). The second modification consists of preserving the superior vesical vessels which are carefully defined when the uterine artery is ligatured at its origin. Figs. 63*a* and *b* illustrate wide removal of parametrium and paracolpos.

After the Second World War, which interrupted the research, 11 of 16 patients were traced and found to be well 5 years or more after operation. There were no postoperative deaths or fistulæ and although the series was small the results were encouraging. Between January 1950, and January 1965, 310 patients received combined treatment with 2 ureteric fistulæ $(0\cdot6\%)$ and 2 postoperative deaths, one from pulmonary embolism and the other from Asian influenza.

Pathological examination of the specimens from 223 consecutive operations revealed a persistence of malignant cells in the uterus in 43% (Figs. 64*a* and *b*), parametrium 8% and glands 22% (Table 46). The fact that 92 of 130 patients (71%) operated on between 1950–58, and 27% with node metastases were alive and well after 5 years was encouraging. With increasing experience the indications for operation were extended until the incidence of combined therapy reached 80% of all patients seen, with a 5-year cure rate of 73%. For all patients registering with the disease it was 57%. Age and associated diseases, previous myocardial infarction, pelvic tuberculosis or endometriosis, are not considered contra-indications provided the patient is active and has a reasonable expectation of life apart from her carcinoma. Many 70 years of age and over are included in the 5-year cures. A gravida 2 of 32, 3 months pregnant,

(a)

(b)

FIG. 63a and b. Wertheim specimens.

(a) in cervix

(b) in myometrium.

FIG. 64. Postirradiation malignant foci.

was found to have an anaplastic carcinoma, mitral stenosis and an associated aortic lesion. She is alive and well 10 years later. Douglas (1961) reported similar results from the New York Lying-In Hospital, where the 5-year cure rate in 156 patients treated by the combined method was 72%. These groups included patients with Stage 1, 2, and a few Stage 3 tumours. Currie (1963) reporting on 400 patients treated by radical surgery with a mortality of 1·25% and a fistula incidence of 2%, stated that: "Many had one preoperative insertion of radium and those with malignant nodes were subjected to further radiotherapy." Of 237 patients operated on more than 5 years previously 178 (75%) were alive and well. When he omitted using radium 4 patients developed secondary pelvic nodules which he concluded were due to implantation of cancer cells. He considers that the chance of cure is halved once the disease spreads into the parametrium.

These collected results establish the following facts:

1. Preoperative irradiation reduces the incidence of local recurrence.
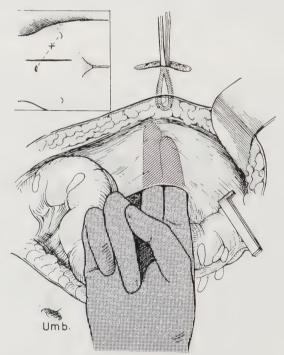
FIG. 65a. Extraperitoneal tunnel for divided colon.

2. A 5-year cure rate of 70–75 % can be achieved even with a high operability rate.
3. Teams trained in the necessary techniques can remove surgically, after irradiation, the primary tumour and the area at immediate risk with a mortality of approximately 1 % and a comparable fistula rate.

Elliot-Smith and Painter (1961) described an extraperitoneal colostomy and ileostomy technique applicable when exenteration is necessary (Figs. 65a and b). They used this method 57 times and
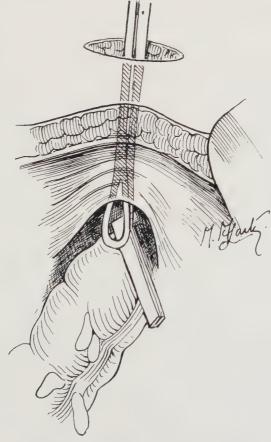
FIG. 65b. Colon entering extraperitoneal tunnel.

found it avoided the dangers of the lateral space associated with conventional techniques and removed one cause of postoperative obstruction. They agree with Goligher (1958) that it reduces the incidence of mucosal prolapse.

Histological examination of irradiated uteri and parametria removed at Oxford 6 weeks after the first application of radium revealed that malignant cells were not always confined to the cervix, even when the clinical diagnosis of cervical cancer seemed obvious. They could be demonstrated sometimes in the myometrium of the corpus (Fig. 64b). The patient from whom this section was taken had a clinically cured cervical cancer and no residual cells in the cervix. Myometrial invasion was unsuspected and was an obvious source of clinically recurrent cancer had hysterectomy not been performed. This could be one explanation of corpus carcinoma developing after apparently successful radium treatment of cervical cancer. Endocervical carcinoma also involves the corpus more often than is commonly realized, which helps explain why the prognosis is worse with carcinoma corporis et endocervicis than with either alone. Kottmeier (1959) reporting only a 41% 5-year survival concluded that radical surgery with lymphadenectomy may be the treatment of choice. He found the ratio of corpus carcinoma to carcinoma corporis et endocervicis to be 4·8 to 1, but the incidence of the latter is almost certainly higher than this. Patients with a cervical carcinoma spreading into the corpus will in most cases be diagnosed correctly only after hysterectomy, which is not performed in clinics using radiotherapy. The prognosis is probably also worse than the 41% Kottmeier reported because undetected spread into the uterine body will be a likely source of recurrence after irradiation for cancer wrongly believed to be confined to the cervix. Although the frequency of corpus infiltration from a primary cervical cancer is not yet known, the fact that it occurs challenges the wisdom of conventional radiation treatment with its emphasis on the cervical ulcer. It supports the strong case for planning treatment so that cancer cells within the whole field at risk will receive doses estimated to be lethal. This principle has been adopted by Fletcher *et al.* (1958), Douglas (1964) and others, including Fichardt (1962) at Pretoria, where treatment by uterine radium is followed a week later by high energy therapy. The claim is made that the method is a good contender "for pride of place in treating cancer of the cervix by radiotherapy" but of 124 patients treated in this way only 82 (66%) were alive and well 30 months later. Thirty-two were alive with residual cancer and 10 had died. In other words, 42 (34%)

failed to respond to irradiation, findings similar to those already reported (Table 46) and giving further support to the concept of combined therapy.

An obvious criticism is that teams trained in the necessary surgical techniques are not available in all clinics responsible for treating cancer, a natural outcome of the emphasis on radiotherapy. It would be foolish not to recognize the changing attitude in thera-peutic trends. Each new Annual Report collating world material records increasing interest in combined treatment. Modern views have been summarized in part by Kottmeier (1963):

> Since the early 1930s radiotherapy has been hotly disputing the mono-poly of surgery, even in easily operable cervical carcinomas. There can be no doubt about the efficacy of either of these methods; but the author's own experience, and that of other gynæcologists has been that in modern practice primary radiation therapy is preferable to primary radical operation. . . . It must however be borne in mind that if satisfactory results are to be achieved it is absolutely essential for radiation treatment to be carried out under the guidance of experienced doctors and in close co-operation with physicists trained in clinical work. Unfortunately this rule is frequently disregarded. It is the author's belief that radiation therapy in cervical carcinomas should always be planned by experienced gynæcologists in close co-operation with radiologists. Under no circum-stances should this rule be relaxed; this is particularly true today since modern technical progress has provided us with much better oppor-tunities for the practice of deep X-ray therapy through the skin.

Within the framework which Kottmeier advocates, surgical teams could be established with the requisite skills to investigate new concepts of combined therapy. Given the will, and the necessary disciplines, the prospects are bright.

Complications of High Energy Treatment

Chau *et al.* (1962) and Kottmeier (1964) considered the complica-tions which can follow the use of megavoltage equipment. Damage to bladder, ureters, small and large intestine, and bones of the pelvis, including the head and neck of femur, have been correlated with conventional methods using radium and external irradiation, and also with high energy techniques. Chau *et al.* claimed that 4,000 r can be given to the whole pelvis followed by approximately 5,500– 6,500 mg./hours of radium to the cervix and vaginal vault with few complications and without prejudicing subsequent radical surgery. Risks are increased by a dose of 6,000 r or more and surgery should be used after such doses only when there is residual or recurrent cancer but if the condition is inoperable 7,000–8,000 r is justified. Severe complications occur in 20 % of patients after high dose therapy.

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With a pelvic dose of 4,000 r the incidence of minor rectal and bladder complications is similar to that occurring after conventional therapy, although protracted dysuria tends to be greater. Negresses are more liable than white women to develop fistulæ, particularly when supervoltage treatment and surgery are combined. Fletcher *et al.* (1962) concluded that 4,000 r to the whole pelvis, followed by the application of radium to the cervix, is safe even when followed by lymphadenectomy or hysterectomy. Rectosigmoiditis occurred in 6 of 158 patients after a minimal dose of 6,000 r. The incidence of small bowel necrosis, sigmoiditis, or fistula formation in 112 patients submitted to lymphadenectomy after 6,000 r or more was 21·5%, and following hysterectomy or exenteration with lymphadenectomy it was 8 in 35 patients (23%). Necrosis of the femoral head occurred as long as 2 years after treatment.

Sigmoiditis

When this condition develops, sometimes associated with proctitis, it gives symptoms within 6–12 months of irradiation in 60% of patients. In 30% it occurs during the second year and only rarely as late as 2 years. It seldom happens after 4,000 r, sometimes after 6,000 r, but the risk increases with the dose. Of 32 patients with sigmoiditis studied by Chau *et al.* (1962), 22 developed the complication in the years 1955–56 but the incidence was reduced with increasing experience. In the acute stage there is irritability of the bowel with mucous stools and sometimes severe rectal bleeding. The affected segment of gut may be palpable and tender, and fluoroscopy demonstrates œdema, rigidity and reduced calibre of the lumen. Obstruction and perforation can occur, or the development of fistulæ into the vagina, bladder, or even into a lymphocyst. If surgery is necessary the alternatives are segmental resection or proximal colostomy which may be necessary prior to resection. Results are satisfactory, unlike those with small bowel necrosis.

Small Bowel Necrosis

This serious complication of high energy radiotherapy has seldom been reported after radium and deep X-ray. Symptoms usually develop approximately a year after treatment, but they can be early or even as late as 2 years or more. A clinical picture of acute intestinal obstruction is common, and delay in surgical intervention carries a grave risk of perforation and peritonitis with a high mortality. As damage is more extensive than appears either radiologically or to the naked eye resection and anastomosis should be at a con-

siderable distance from the affected segment but union often fails because of devitalized bowel. Fistulæ, which may be multiple, occur frequently and open into the vagina, peritoneal cavity or bladder. Their management is difficult and prognosis grave. Necrosis after 6,000 r or more was a complication in 14 of 434 patients but it happened twice when surgery followed a dose of less than 6,000 r.

Less serious damage with mucosal ulceration causes intermittent diarrhœa, cramps, and occasionally melena. Spontaneous recovery is usual. X-ray evidence is essentially that of any small bowel inflammatory process with œdema, areas of stenosis and bizarre configurations of the lumen.

Fistulæ

These may follow bowel necrosis, particularly after 6,000 r or doses exceeding this, and the risk is increased by surgery. In the series of 434 patients there were 14 with vesico-vaginal, recto-vaginal and uretero-vaginal fistulæ, in addition to 2 associated with sigmoiditis and 4 with small bowel necrosis.

Bladder Ulcers

These usually appeared from 6 months to 2 years after treatment but some developed even after 3 or 4 years. Persistent dysuria and hæmaturia is difficult to control. Ulcers are usually on the trigone, but occasionally in the dome of the bladder. This complication did not develop after 4,000 r but with bigger doses and following intra-uterine radium with extreme anteflexion of the uterus. Treatment is conservative with blood transfusion, control of infection, anti-spasmodics and analgesics. Cortisone may help in some cases. Cauterization of the ulcer to stop bleeding was sometimes necessary.

Summary

Supervoltage therapy can have serious complications which are unlikely to occur with a dose of 4,000 r. They increase when 6,000 r, or larger doses, are followed by operation.

Suggested Scheme for Treatment of Carcinoma of the Cervix

Whatever method of treatment is adopted the general condition of the patient is important, with control of anæmia and infection. From the preceding review of publications selected from an extensive

literature to reveal current trends the following suggestions are made:

1. Patients with uterine cancer should be concentrated in clinics staffed by gynæcologists and radiotherapists with the necessary equipment and ancillary services to offer the benefit of modern therapeutic weapons.
2. The primary treatment of carcinoma of the cervix should be by irradiation.
3. The whole area at risk should be treated. This includes the entire uterus, body as well as cervix, the parametrium, at least the upper half of vagina, and the pelvic lymphatics.
4. The available evidence suggests this can best be accomplished by high energy treatment to give a dose of 4,000 r to the whole pelvis, associated with 5,000–6,000 mg./hours of radium application to the cervix and vault.
5. Surgical teams trained in the necessary techniques can improve the prognosis by performing postirradiation radical hysterectomy and lymphadenectomy.

Carcinoma in Pregnancy

Fletcher *et al.* (1962) found that the prognosis for carcinoma of the cervix was worse in pregnancy and in the year after delivery. The worst results followed delivery through a malignant cervix. In their series the risk of nodal metastases appeared to be increased by pregnancy. They adopted the following therapeutic routine in the first two trimesters and the puerperium. A dose of 4,000 r was given to the whole pelvis by external irradiation over a period of 4 weeks and subsequent treatment was adjusted for each patient. In the first trimester abortion usually occurred spontaneously after 2,000–3,000 r, and in the second trimester it usually occurred before treatment was completed by which time the uterus had involuted sufficiently for radium to be applied. On 4 occasions abortion did not occur in the second trimester and vaginal irradiation followed by hysterectomy was performed. In the third trimester classical Cæsarean section was followed 3 or 4 days later by pelvic irradiation. After 4,000 r involution was usually sufficient for radium to be applied. In the puerperium, or in the first year after delivery, treatment consisted of 4,000 r to the whole pelvis followed by the application of radium.

Fluhmann (1961) agreed with Fletcher's views on treatment in the first trimester, and stressed the danger of inducing abortion before beginning irradiation. He quoted Heyman as stating that the 5-year survival rate was reduced by this procedure to 11 % compared with 56·7 % when spontaneous abortion followed radiation therapy. The analogy between this and surgery before irradiation is obvious and is an argument against operating without preliminary irradiation even in early cases. During the second trimester Fluhmann considered that abortion was less likely to occur and advised hysterotomy before beginning treatment, but Fletcher's experience suggests this is not often necessary. During the third trimester Fluhmann emphasized that delay to improve the prognosis for the infant prejudices the outcome for the mother and advised classical Cæsarean section followed by irradiation.

A useful point of technique during classical section in these patients is to mobilize the utero-vesical fold and bladder sufficiently prior to opening the uterus to permit suturing the peritoneum above the incision at the end of the operation. This makes the incision extraperitoneal and reduces complications including peritonitis.

The Future

Increasing emphasis must be given to providing facilities for screening the female population at risk and to teaching the profession and the public how to use these services with maximum efficiency.

Megavoltage techniques are still in their infancy. There is a difference of $2\frac{1}{2}$ times in the reaction of the oxygenated and anoxic malignant cell (Ellis, 1963). Possible applications of either increasing oxygen tension in malignant areas, or decreasing it in the body as a whole during irradiation have still to be fully explored. The use of substances to sensitize cells to the effect of radiation is being explored (Mitchell, 1960). Contributions which chemotherapy and hormones may make are still relatively unknown, but a recent advance is the ability to synthesize preparations of great potency for specific purposes. An important research project concerns the effect on malignant cells of fractionating treatment. This involves close correlation between radiobiological and clinical study and is an argument in favour of centralizing the investigation and treatment of uterine cancer. The ultimate goal is the elimination of carcinoma of the cervix.

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THE PATIENT, THE DOCTOR AND THE LAW

"There but for the grace of God go I."

If every doctor accepted the truth of these words when he heard of complaints and allegations against colleagues the prestige of medicine would benefit. Criticism, whether outspoken or merely implied, can encourage a patient's dissatisfaction and is therefore an avoidable factor in litigation. When others are in trouble it is easy to adopt the attitude of "It could never happen to me", without pausing to consider how their predicament arose. Study of the basic reasons for this, in an attempt to learn from mistakes, can help to avoid future difficulties. The practical application of this prin-ciple has been demonstrated in Chapter 1 in relation to maternal mortality.

A review of the medico-legal position at the present time in Britain, the Commonwealth and America, discloses some important facts common to all as well as differences peculiar to each. They apply to every aspect of medicine and for this reason examples will not be taken exclusively from obstetrics and gynæcology to illustrate the dangers to which a doctor is exposed. It may seem strange to devote a chapter to this subject in a book dealing with recent advances. The excuse, if any is needed, is that standards of medical practice are influenced by more than therapeutic techniques. Improvements in these do not necessarily guarantee better care of the patient. Anything that does do so constitutes an advance, even if it be no more than a rediscovery and emphasis of truths once established but since forgotten.

One of the most important of these, concerns the controversial issue of the doctor-patient relationship. Those with a wide experi-ence of medical and dental litigation know that annoyance and dissatisfaction starting at personal level often precede criticism of professional skill. "DOCTORS NEGLIGENT AND INHUMAN, SAY PATIENTS" and "GUINEA PIGS FOR DRUGS" were Press headlines in England on September 4th, 1964, reporting an analysis of 525 alleged complaints by patients, including breakdown of communi-

cation between patient and doctor in 14% and discourtesy, rudeness and indifference in 12%. There are unhappy people who cherish grievances and when their disquiet has a medical background it is the more necessary that complaints should be investigated fully and impartially before conclusions are drawn and reports published. This need is illustrated by the fact that in 1963 81% of official complaints to local executive councils against general practitioners were proved to be unfounded as far as violation of terms of service was concerned. Allegations of negligence and of using patients as guinea-pigs are grave charges and affect not only doctors directly concerned but the reputation of the whole profession.

If a doctor is not informed that reports concerning his integrity or professional skill have been made to a third party he is unable to defend himself, and those to whom the charges were made cannot investigate them impartially. This injustice was allowed to pass without Press comment and reflects the medico-legal climate in Britain today. Winds of change are not confined to Africa, and doctors should consider the implications of this changing scene before it is too late.

The fine tradition of British medicine had been built on a basis of dedicated voluntary service in the great hospitals of the country, and the bedside manner was as important in the wards of Guy's Hospital or Leeds Infirmary as in a private clinic in London, W.1. It implied a personal doctor/patient relationship essential to the establishment of the respect and confidence without which medicine could easily become just another nationalized industry. Many criticisms now made against the profession are based on a decline in the standard of this relationship. The term "bedside manner" is no longer used officially and to be with it in 1964–65 you speak of "communication" in hospital or practice. An acceptable bedside manner allayed fears and anxiety and created confidence. This sometimes required explanations which were simple for the patient to understand, but these were often not wanted and were then neither necessary nor wise. It still is important to consider the possible patient reaction before discussing details of treatment and prognosis. The bedside manner and good communication are exactly the same in their contribution to medicine, and their neglect can distress the patient and endanger the physician. Their importance in litigation will increase as the public becomes progressively better informed on medical matters.

A breakdown in communication can constitute an avoidable factor in litigation, and recognition of this by the profession leads

to improvements in medical care. Press, radio and television inform the public of changes in contemporary medicine and as a result patients may feel better able to protest at what they believe is unsatisfactory professional conduct or service. As illustrated in Chapter 1, the best current practice of yesterday may provide a basis for litigation if used today. Failure to adopt new ideas or techniques can result in allegations of negligence, and a doctor must keep himself abreast of generally accepted methods.

A small minority of patients will instigate legal proceedings hoping for financial gain without the risk of loss.

A man with a malignant parotid tumour and facial palsy was referred to an eminent surgeon who successfully extirpated the growth. Later in the local pub, the patient told his friends of the operation. A stranger who offered him a drink commented that the face was "in a bit of a mess", and this could be worth a lot of money without any cost to the man himself. If he was prepared to take legal action for damage this would all be arranged for him. He agreed.

The surgeon received a lawyer's letter alleging negligence as a result of which "their client had suffered permanent paralysis and disfigurement". Detailed records of the case, including pre and postoperative photographs revealed the charge as being entirely unfounded and nothing more was heard of it.

This illustration emphasizes two points:

1. It is unwise to count on the gratitude of patients.
2. The need to keep accurate records containing all essential details. The more difficult the problem the greater the necessity for this. Photographs can sometimes, as on this occasion, be worth more than pages of notes.

A postmenopausal woman of 52, citizen of a foreign country, had been married for 15 years without consummation. The declared reason was a deep fear of pregnancy. When her husband retired they decided to fulfil a long-cherished ambition to visit Britain and Europe. While in Paris they went to the Moulin Rouge, and that night intercourse was attempted. It was immediately resented and although she was postmenopausal the woman believed she had conceived. When slight bleeding occurred later the conviction became deeper and mental distress was acute. A French gynæcologist refused to rule out the possibility of pregnancy and the couple, now desperate, crossed to England. In the early morning they consulted a general practitioner for bleeding "due to an abortion". The practitioner realized the case was difficult and asked a gynæcologist for an immediate consultation.

The relevant history given by the anxious husband was recorded on a dictaphone, from which the case record was typed. Examination disclosed hypertension with auricular fibrillation and a compensated heart. This was a surprise to all concerned. Vaginal examination was impossible as

consummation had not occurred and the patient was *virgo intacta*. Rectal examination disclosed a bulky mobile uterus and a left-sided ovarian tumour. The provisional diagnosis was made of a functioning ovarian tumour, the implications of which were explained to the husband while his wife dressed and then to both together. A dictaphone record was made of this.

Relief at not being pregnant was so profound that the prospect of surgery caused little concern. It was explained that vaginal examination would be necessary under anæsthesia and if the findings were confirmed the uterus, ovarian tumour and other ovary would be removed. Because of the possibility of either the tumour or the uterus being malignant a bed was arranged urgently under the National Health Service. A consultant physician made a special visit to hospital to assess the cardiac condition, as did a consultant anæsthetist. They agreed on spinal anæsthesia followed by postoperative anticoagulant therapy because of the increased risk of embolism.

Plans worked smoothly and the patient was discharged on the 10th day for convalescence in an hotel. Their intention was to return home by air, but the contribution which a sea voyage would make was mentioned and although reservations were almost impossible to obtain the hospital procured suitable accommodation on a fine ship. The Health Service appeared to have done its work not only well but humanely.

From the first port of call came an air letter asking for a medical report to be forwarded to await them at their destination giving details of the operation and why it was done. This was sent. In return a letter arrived stating that the report was false; that no permission had been given for an abdominal operation; that removal of the uterus had been unnecessary, and as a result of the operation married life was now impossible. Legal action was being taken for assault and negligence.

A copy of the detailed notes made at the interview, examination, operation and during postoperative recovery proved the charges to be completely false. Nonetheless, the case is a warning of unjustified claims from unexpected sources. Accurate records are always a safeguard and particularly when litigation arises from misunderstanding or malice. When the acute episode of illness is over and anxiety is forgotten a small but increasing number of patients seek to convert real or imaginary mishaps or complications into hard currency. This fact introduces with some urgency the need for a reappraisal of the doctor/patient relationship. No longer can a doctor expect his patient to regard his advice and treatment as infallible. It is unwise for him to take this view of them himself.

"So far as power and discernment shall be mine, I will carry out regimen for the benefit of the sick, and will keep them from harm and wrong."

In spirit if not on oath the young doctor as he commences practice accepts these guiding Hippocratic principles but though his prime duty is to protect his patients he must also protect himself. These two requirements are seldom incompatible.

A team of doctors and nurses by hard work and devotion to duty may, after hours of strain, see an apparently moribund patient revive. If an ill-chosen injection site results in nerve injury, however trivial, or injudicious heat produces a burn, however well concealed from public view, the team could be defendants in a legal action. The charge would be negligence as a result of which "our client suffered needless pain, disability, and disfigurement". If the injury was confirmed the charge of negligence would be substantiated. Defence expenses would be considerable and would have to be borne by the defendant, even if the plaintiff lost the case but had been awarded legal aid.

Desperate situations demand desperate measures to meet them, but medical and nursing discipline should be such that even in an emergency potentially dangerous procedures should not be adopted when equally effective but safer ones are available. If a drug acts when administered intramuscularly it will do so whether given into the deltoid, the gluteus maximus, or the quadriceps. As no nerve can be injured by injection into the outer aspect of the thigh this site is safer for both patient and doctor. *The arm should never be used for intramuscular injection* and to do so risks injury to the patient and litigation in which there is no defence.

The several institutions founded in Britain for the sole purpose of protecting the professional interests of doctors and dentists have expert legal opinion available and a wealth of experience with which to deal most effectively with claims, whether justified or not. The protection they offer is also available to doctors in Common-wealth countries. Those who have qualified in the United Kingdom or the Republic of Ireland are given unlimited indemnity, as from 1st January 1966, for an annual premium of £6. Newly qualified practitioners have the annual premium reduced to £3 for their first 3 years of membership. Doctors who have qualified abroad but are practising in the United Kingdom or the Republic of Ireland and have been granted full registration with the General Medical Council pay an annual subscription of £8 for the first 5 years, after which the premium of £6 is the same as for doctors qualified in the United Kingdom or Ireland. Practitioners who have qualified abroad and have been granted provisional registration with the General Medical Council pay £3 for the first year of membership, £8 for the second, third, fourth and fifth years, and subsequently £6 per annum. For overseas membership (which excludes practice in the United States of America) the premium is £5 for the first year of membership of a newly qualified practitioner, but £8 for subsequent years. In America

the situation is very different and for a limited indemnity of three claims of 100,000 dollars annually the premium required varies from 99 dollars in Vermont and Nebraska to nearly 450 in California. These rates are offered by one insurance company to Fellows of an American College of specialists. As insurance premiums tend to be fiercely competitive it is unlikely that terms much more favourable could be secured. There are even variations in the scale of premiums within the same state in America. For example, rates are higher in metropolitan than in suburban or rural areas. It was estimated by *New Medica Materia* (1963) that in 1961 17,000,000 dollars were paid in medical insurance premiums in the United States and this figure could well be too conservative.

The discrepancy in these premiums is amazing, but the implications of the varying scale are important when considering the future of doctor/patient relationships. The rates quoted are assessed, like all insurance premiums, on the risks the company accepts and will be raised if business becomes unprofitable or lowered by competition if the profit margin warrants it. The risks the company takes when a doctor pays his premium are an indication of the risks to which he himself is subject. In America therefore there is the anomalous position that the same doctor would be required in one state to pay 5 times the premium for which the same insurance company would provide him with an identical indemnity in another state. This means that the risk of litigation is related more to the medico-legal climate of the community than to the qualifications and experience of the doctor. To a lesser extent the same is true within the British Commonwealth. The comments of an American lawyer experienced in legal work are illuminating:

You will see that the rates are significantly different depending upon the locale in which the doctor practises. I think that one of the things that tends to a degree to lessen the total number of malpractice cases in a rural community is the fact that members of the different professions know one another a great deal better in those communities, and there is also a closer relationship between the patients and the physicians. More and more in these days of specialization in the metropolitan areas the doctors usually see their patients on a short term basis and there is not the tendency to be as forgiving of what is thought to be a mistake (personal communication).

In places such as America and some Commonwealth countries where negligence charges are usually tried by jury there are cases in which the chance of the defence being successful is less than if the facts of the case were decided by a judge. Counsel for the defence therefore prefers not to have a jury, while Counsel for the plaintiff

welcomes one. Total damages of $1,000,000 and more have been awarded in America and there have been a number of verdicts involving $500,000. Awards in British courts have so far been smaller but thousands of pounds are often involved. Just as violence tends to beget violence, so there is a tendency for one successful negligence claim to encourage another. Herein lies the probable explanation of the high premiums necessary for even limited indemnity in some places. A survey sponsored by the Californian Medical Association revealed that 30.1% of the surgeons in two large hospitals were insured against damages of over $300,000. Doctors practising in Britain and Commonwealth countries are fortunate that unlimited indemnity can be provided for a small annual premium. Whether this happy state will continue will depend largely on themselves.

A review of the present position of medical litigation indicates that whereas many unreasonable claims arise, and if skilfully handled are disposed of without ever entering court, the greatest safeguard to both patient and doctor is a high standard of professional care. If this is maintained a practitioner has nothing to fear and is more likely to meet the lawyer on the golf course than in the courts. This being so, a brief examination of the problems which commonly cause trouble can furnish a guide to practice and promote a greater margin of safety for patient and doctor alike.

There are hazards common to all who practise medicine irrespective of age, skill, or experience, and there are others of particular importance to certain sections of the profession. The clinical incidents giving rise to trouble may be very different but have a common factor. A dentist extracting the wrong teeth or a surgeon amputating the wrong finger both demonstrate a lapse into carelessness. Both are human and therefore fallible. It is fortuitous to what extent a clinical mistake may involve the patient in distress and disability, and a doctor in litigation. Success or tragedy can depend on one swift decision and chances should be taken only as carefully calculated risks which *should be duly recorded in the notes;* for example, when in a grave emergency O negative blood is transfused without cross-matching.

A wise man profits from the mistakes of others. In the Maternal Mortality Enquiry (Chapter 1) knowledge of avoidable factors improved results but there is an important corollary. For efficient antenatal care to halve the risk of death to a pregnant woman its importance must be realized by both doctors and patients. All complications of pregnancy are not avoidable, but should disaster

occur the patient or her relatives may consider that it was due to medical neglect. Whether this is true or not it could be the basis of a charge of negligence. For example if a woman died of eclampsia and her husband knew that she had been seen only once a month and had been treated for hypertension by resting at home he might attribute her death to inadequate professional attention. The fact that the death would be regarded as one with an avoidable factor would strengthen his case. Any defect in the standard of medical care making it less than could reasonably be expected of current established practice might be used as the basis of a negligence claim. Whereas failure to record the blood pressure of a pregnant woman would not have been negligent 25 years ago it certainly is today, as would be failure to take appropriate action if it were recorded and found to be abnormal. Failure to estimate the hæmoglobin of a patient before operation or to take necessary precautions if it revealed anæmia would today probably be regarded as negligence, although 10 years ago it would not. Changing trends in disease are important in their legal implications and the more effective the remedy the greater the disaster if it is not employed. Negligence established in relation to a patient dying from cancer would be assessed in court on an entirely different basis from the damages likely to be awarded if congenital syphilis were the result of a doctor failing to test the Wassermann and Kahn reaction of a pregnant woman. In communities in which venereal disease is increasing, failure to detect it is an avoidable factor of serious and increasing potential. On the other hand, a positive Wassermann does not justify the final diagnosis of syphilis and under some circumstances legal repercussions would be likely to follow a mistake of this nature (Chapter 3). Cervical screening techniques carry a medico-legal risk. As emphasized in Chapter 8 these methods do not diagnose cancer, nor do they exclude its presence, but select with a small margin of error those patients who require further investigation. When carcinoma of the cervix is clinically recognizable the cytology test is least accurate and carries a 10% error. It is therefore clinically and legally dangerous to state that a woman has cancer because the test is positive, or that there is no cancer because one test is negative. If a suspicious cervix, which later proves to be malignant, is not submitted to biopsy because the cytology test is negative it would be hard to defend the doctor against a charge of negligence.

From these examples it will be clear that many, probably most, negligent acts whether related to errors of omission or commission

will pass unnoticed and it is only when complications arise that medico-legal repercussions may follow. If the existence of avoidable factors can be proved there will be reduced prospects of successful defence. There are five lessons a doctor should learn. They are:

1. To endeavour at all times to maintain the confidence of the patient
2. To keep accurate, legible and up-to-date notes correctly dated.
3. To be meticulously accurate in all reports and certificates and to sign nothing he would not be prepared to swear on oath was correct to the best of his knowledge.
4. To presume nothing professionally.
5. To avoid taking final responsibilities beyond his experience except in emergencies.

These guides to practice are designed primarily to safeguard the patient but by following them a doctor also safeguards himself and because of their importance they will be considered in more detail.

Maintaining Confidence

The patient who feels that the doctor is casual, careless, or inattentive is more likely to resort to legal proceedings if he believes that professional skill has been inadequate than is one who has good reason to know that the doctor has been genuinely interested and unsparing in his efforts to help. The primary role of the doctor is to advise, and except in certain emergencies he has no mandate to act without authority from the patient. This implies that sufficient explanation is given to make a reasonable decision possible. The more the patient understands what is being done and why, the less the change of subsequent dispute. If agreed treatment is altered the reason should be explained. For example, a woman was informed that Caesarean section was necessary but later the doctor changed his mind and delivered a stillborn infant vaginally. Legal proceedings followed. If the reason for the change of plan had been discussed with either patient or husband and a record made in the notes to this effect there would have been less chance of a dispute, and the defence would have been stronger.

A pregnant woman with mitral stenosis which had complicated previous pregnancies was seen by a physician, a cardiologist and a gynæcologist. It was agreed that the pregnancy should be terminated and the tubes tied. She accepted this advice and hysterotomy was performed but because

her condition caused concern under anæsthesia and there was extreme vascularity the surgeon decided not to perform his usual method of wedge resection of the cornual end of the tube but crushed it and tied a silk ligature. The patient failed to keep her postoperative appointment and was not told of the difficulty which had arisen. She conceived and took action against the gynæcologist for negligence. The reason given was that he had not informed her or her husband that he had used a technique in which he was not confident nor that ste ilization was not 100 % effective. The defence was that the patient had not kept her appointment with the gynæcologist whose usual rule was to explain relevant details at the postoperative examination and not in the ward where overcrowding made private discussion impossible. This defence was successful.

The wisdom of discussing with a patient the implications of proposed treatment is illustrated by the following dilemma which is likely to become more of a problem in the future.

A gynæcologist planned to graft healthy ovarian tissue into the pelvis of a young woman whose ovaries had been removed. The implication was that if the patient conceived there would be difficulty in deciding whose child it was. Counsel ruled that the child would be illegitimate on the basis that by definition a legitimate child is one conceived in wedlock by the fertilization of the wife by the husband. He maintained that there was no doubt that a child conceived by donor insemination is illegitimate, and he could see no distinction between the position of a child conceived following fertilization of the ovum by the sperm of a donor and a child conceived by the fertilization of a donor ovum by the sperm of the husband.

When diagnostic procedures (which though desirable are not essential) carry a risk of serious complications, a difficulty arises. It is obvious that they should not be undertaken lightly, but it is not easy to determine the extent to which dangers should be discussed with the patient. The less essential the proposed investigation, and the greater the risks, the more necessary it is to inform the patient or a close relative of what is proposed, and the possible repercussions. If the incidence of unpleasant sequelæ for the particular procedure is unduly high it would not be regarded as conforming with established practice. Any suggestion of experimentation would be unfortunate in the event of litigation, but if, for example, a leg has to be amputated because of embolism or thrombosis following an aortogram, the doctor must be able to convince a court that the investigation was necessary. This could be difficult in some circumstances, as, for instance, in the diagnosis of placenta prævia (Chapter 1). Problems associated with surgical as opposed to traditional conservative treatment for puerperal or postoperative pelvic venous thrombosis come into this difficult category.

Accurate Records

Reference to the necessity of keeping accurate records may seem obvious but needs no apology. The standard of these is often disappointing and many claims are lost for the defence, or settled out of court, when relevant facts are missing from the notes. Adequate records serve a triple purpose:

1. At the time of writing they give the opportunity of second thoughts on what has been observed, decided, advised and performed. This will sometimes reveal errors of omission and commission in time for them to be corrected.
2. They help to promote concise and accurate thinking and recording. Particularly is this so in hospital practice if someone more experienced reads the notes and commends or criticizes them. It is good discipline to read them yourself and be equally critical.
3. They save trouble if disputes arise. However certain a doctor may be that his memory is accurate, his chance of persuading others is doubtful when there is a conflict of evidence. If the case involves a baby or a child and is heard before a jury accurate records are even more important because a child in court is likely to arouse more sympathy than a doctor defending his professional skill.

In medicine there are many unpredictable factors which influence adversely or otherwise the progress of a patient. It is important that all relevant details at all stages of a patient's care should be noted carefully and legibly for precise records dated and signed can scarcely be challenged. A shilling Biro used at the right time can save thousands of pounds later. If a doctor cannot read his own writing it is unlikely that others will succeed, even if they are willing to try. Every note should be an accurate, legible record which would make clear to an independent reader exactly what was happening, even though he did not see the report until years after the event. Clinical notes which do not fulfil this requirement are inadequate. In the hospitals of tomorrow records will be typed from dictaphones. They will be easy to read but unless they are checked they may be inaccurate. As it will not be possible to identify the author by his writing it will be even more important for him to check, sign, and date the final copy.

A useful exercise designed to improve the standard of medical records can be commended. At the beginning of his pre-registration

year every resident should be asked to choose a subject for investigation. It matters little what the subject is, appendicectomy, pneumonia, or anything else that appeals. He prepares a short paper based on the records of a small number of these patients. He would find some illegible, many incomplete, and some obviously inaccurate. He would be fortunate if he found one or two in a dozen which he would be proud to have written. This exercise emphasises the purpose for which notes are made and stimulates the young doctor to do the job properly himself. New recording techniques with the utilization of automation in the hospitals of the future make the need for efficient primary recording even more urgent.

Meticulous Certification

An inaccurate certificate can be produced years later to the discomfort of those who signed it and false certification is a subject in which the General Medical Council is interested.

Instructed by the High Court a gynæcologist examined a man whose wife petitioned for nullity on ground of non-consummation "to report in writing whether (a) he is capable of consummating the marriage, and (b) if incapable, whether his impotence can be cured."

The husband admitted non-consummation which was not surprising for examination revealed that he was in fact a woman with a normal vagina and rudimentary uterus. At birth he was registered as a female but years later an endocrinologist and a physician signed an affidavit affirming that a mistake had been made and the correct sex was male. A new birth certificate was issued. He maintained that he had lived with his wife before marriage and that she was fully aware of his physical inability and in view of the birth certificate he was distressed that his sex was again challenged, with the possible implications of press publicity, loss of employment, and readjustment to life.

The physician who had signed the affidavit expressed a wish on the day of the court proceedings to meet the gynæcologist. In the corridor outside the court he stated that he was not proposing to contest the evidence concerning the female nature of the husband's genital apparatus. Hearing this statement Counsel for the petitioner was much concerned and reminded him of his sworn affidavit stating that the sex was male. The physician admitted that he had not made a pelvic examination but was concerned with the psychological aspect of the case. The endocrinologist had been interested in endocrinology! The amazing situation was therefore apparent that in spite of a uterus and vagina this individual had the unique distinction of sexual metamorphosis by certification because of a statement made by two eminent doctors, neither of whom had made a pelvic examination. The legal reaction was swift and at the last minute the case was withdrawn.

Gynæcologists are sometimes asked for certificates required for the breaking of Trusts. The information needed usually concerns

inability to bear a child and great care is necessary before giving an assurance on this point (Chapter 7). After hysterectomy or the menopause the position is usually simple though not completely free from danger, as illustrated by the following case record.

A woman aged 35 was referred to a gynæcological clinic with the diagnosis of an ovarian cyst following hysterectomy. Examination revealed a 16-weeks' pregnancy, a diagnosis she refused to accept, as did her general practitioner who sent a copy of the letter he received from the hospital to the surgeon who performed the original operation. His cryptic reply rejected the diagnosis as ridiculous.

Twenty-four weeks later the infant was born after a normal labour. Explanations to account for the confusion are irrelevant to the fact that this woman produced a child in spite of her story of a hysterectomy. The moral is clear. A patient's history, however genuine it *appears* to be, *must* be confirmed by examination before an opinion is given and a certificate is signed.

Similarly, after alleged tubal ligation the history of operation provides doubtful grounds on which to certify that pregnancy is impossible. Many authentic conceptions have occurred following this operation and it would be essential to know the exact details of the technique used, and the experience of the surgeon. If reasonable doubt exists as to what was done a necessary precaution is to perform hysterosalpingography. Even this is not necessarily conclusive. The only positive evidence is demonstration of tubal patency confirming that the operation if performed was unsuccessful. A block at the level of the alleged ligatures (if this is recorded in the notes) would be reasonable support, but could be misleading (Chapter 7), and would provide a doubtful basis for a report.

Errors are easily made:

A woman of 38 had a history of an ectopic gestation and two Cæsarean sections, at the second of which her tubes were allegedly tied. Two years later she conceived. Her distress and that of her husband would undoubtedly have involved the surgeon in litigation had the situation not been handled with tact. He was experienced, skilful, and careful, which made the diagnosis of pregnancy the more difficult to understand. His operation notes were obtained and the explanation became clear. The second Cæsarean was difficult because of adhesions following the first two operations and when the tube on one side had been displayed and ligatured the abdomen was closed, assuming that the other tube had been removed. The notes recorded that the tube had been conserved at the time of the ectopic operation. By failing to read this and to assess carefully the relevant available information the surgeon made an unjustifiable assumption and left a patent tube, although the patient and husband were told that pregnancy was no longer possible.

Guidance on how medical reports requested from hospital authorities should be handled is given in Circular (59) 88 issued

by the Ministry of Health. This is designed to safeguard the doctor under English law, but there would be wisdom in following its advice in any country. Help is given on the release of information concerning patients who are taking, or contemplating, legal action against the hospital, or against a third party. There are two types of case about which hospital authorities are likely to be asked for information.

1. Where the patient or a relative is instituting, or thinking of instituting, an action against the hospital authority, or against a member of its staff, or both.
2. When a patient is, or may be, engaged in litigation with a third party over proceedings being taken either by or against the patient. In this case neither the hospital authority nor its staff is directly involved. This could be for example a claim for damages following an accident, or divorce proceedings following a patient's admission to hospital with an abortion.

Every request for information must be considered on its merits, but when it is required about diagnosis, details of treatment, condition on discharge, or prognosis, the practitioner in charge of the patient's treatment in hospital should be consulted. Even a request for extracts from case notes should be referred to him. If it appears that he may be involved in litigation he should notify at once the Protection Society or Union of which he is a member, forward the necessary details, and await advice. When the request for information emanates not from the patient or his representative, but from some other party no information of any kind should be supplied until the patient's written consent has been obtained, unless a witness or document has been the subject of a subpœna.

A difficult situation arises if an employing authority such as a Management Committee or Board requests a confidential report on a colleague, either professional or lay. If for any reason the doctor feels obliged to act on the request he would be wise to take advice from his Protecting Society before sending a report. Issues of libel, slander, and privilege could all be involved and expert guidance is needed.

Definitions

Libel (the written word) or *Slander* (the spoken word)

These consist of an untrue statement published concerning someone which "lowers him in the eyes of right thinking people". Not all libels or slanders are actionable. Publication may be in circumstances for which "privilege" can be claimed.

Privilege

This may be absolute or qualified. Absolute privilege is limited to a narrow group, including statements prepared in connection with legal proceedings. Qualified privilege covers a wider field. It is a subject on which there have been many legal decisions and guidance can be given only on broad principles. The following two classes of statement illustrate but do not exhaust these.

1. A statement made in the discharge of a public or private duty.
2. A statement made on a subject in which both the maker of the statement and the person to whom it is made have a legitimate common interest.

If the publication of a libel or slander comes within the class of those to which qualified privilege is attached it will still be actionable if it was inspired by "malice". This is a technical term and can mean more than ill will, although an untrue and defamatory statement published on a privileged occasion because of ill will toward the person defamed would be actionable. The term "malice" is difficult to define and has been interpreted in many judicial decisions. Modern text books tend to sum up the position by stating that it means "any improper motive".

It follows therefore that if as a result of a report issued by a doctor the plaintiff feels aggrieved and claims he had been libelled, the doctor would need to prove that the occasion had been a privileged one. Even so the plaintiff could endeavour to establish malice on the part of the defendant. This can be done in a variety of ways, ranging from producing proof of actual ill will to arguing from the basis of extravagance of language used in the alleged libel, or recklessness on the part of the defendant in failing to establish the truth of the statements made in his report.

For these reasons before issuing a report of this nature it is wise to take the following precautions:

1. To submit it only through the proper channels as a confidential document.
2. To establish that the facts alleged in the report are true to the best of the writer's knowledge and belief.
3. To use simple language and avoid terms which could be construed as extravagant.
4. To be as certain as humanly possible that no motive inspired the writing of the report other than that of doing one's proper duty.

A doctor must be prepared to swear on oath that anything he puts in a certificate is to the best of his knowledge completely accurate. This implies that he should have collected all the relevant evidence before giving his opinion. When a doctor is confronted by a letter or report written by a patient or other party and considered by him to be defamatory he is wise to take no action, verbal or in writing, other than to consult his Protection Society or Defence Union for their advice.

Presume Nothing

One of the first lessons a medical student must learn is that a doctor should presume nothing nor take anything professionally for granted. The case of the woman pregnant after an alleged hysterectomy illustrates this. Many tragedies causing disablement or death and worrying and expensive claims for negligence arise from unwarranted assumption on the part of the doctor. Trichloracetic acid and cocaine may look the same in the container but their effect on delicate tissue is vastly different. A solution of 1 in 500 perchloride of mercury may reduce the chance of implantation of cancer cells during bowel resection, whereas a 5% solution can kill the patient. To presume that somebody else has not made a mistake without checking such important details as the name and blood group before transfusing can result in disaster. To make the double assumption that local anæsthesia is safe and that the liquid used is $\frac{1}{2}\%$ zylocaine when in fact it is 2% can cause death. To presume that the right patients are coming in the right order for the operating list without carefully checking in detail before beginning to operate can result in untold tragedy and claims for negligence which cannot be defended. To report to a third party that a single woman is pregnant when she is not, or that an innocent patient has syphilis merely because the WR is positive would be medically unjustified and could be legally dangerous (Chapter 3).

Responsibility

The extent to which responsibility should be referred and accepted can be difficult to decide. The careful clinician recognizes when dangers lie ahead and takes the necessary steps to safeguard both his patient and himself. Failure to ask for help can be an avoidable factor in maternal deaths (Chapter 1) and a preliminary to litigation in other fields of medicine.

A young surgeon performed an extensive pelvic operation for genital cancer, and trauma to the ureters resulted in fistulæ. It was alleged that he had not recognized the serious implications of post-operative symptoms, took no effective action to deal with the situation, and delayed sharing responsibility with a more experienced colleague. A claim for heavy damages was settled out of court.

Mills (1963) analysed 1,000 malpractice cases covering the entire field of medicine and found that most (25%) were surgical and 17% gynæcological. Disputes arose because of infection, hæmorrhage, alleged unnecessary operation, and fistulæ. Complaints of delay in recognizing operative injury and of its subsequent treatment are relatively common and emphasize the necessity of doctors being aware of their limitations. A fistula can be difficult for an expert to cure and repeated unsuccessful attempts increase the patient's distress and the risk of litigation.

A woman developed a recto-vaginal fistula following vaginal hysterectomy. Her confidence in the surgeon was so great that she submitted to twelve attempts to repair the damage, after which the hole was so large that formed stools were passed per vaginam with resultant curtailment of all social activities. The surgeon at no stage suggested a second opinion and after the twelfth operation informed the patient that the condition was incurable. Years later the fistula was closed by another surgeon, whose tact prevented legal complications.

This illustrates three important points; no-one is infallible, it is wise to have a second opinion before pronouncing a case hopeless, and if a patient has complete confidence in her doctor legal proceedings are unlikely even when things go hopelessly wrong.

Dual Responsibility

Many anæsthetic preparations are potentially more lethal than the original chloroform and their margin of safety is proportional to the skill of the doctor who administers them. Except under exceptional circumstances there is no longer any excuse for a doctor to give a general anæsthetic and then to operate. Epidural, spinal and caudal anæsthesia have their peculiar hazards and require skilled observation and occasionally prompt treatment which ideally should be the responsibility of an anæsthetist. If complications arise and litigation follows when a doctor is acting in the dual capacity of surgeon and anæsthetist his defence is difficult.

An extension of this principle is seen in other aspects of obstetrics and gynæcology. In Chapter 1 the need for team work in efficient

antenatal care was emphasized. Failure of an obstetrician to obtain the opinion of a physician or cardiologist when there is reason to suspect heart disease would be considered an avoidable factor if death occurred, and could be the basis of legal action. While it is true that every patient is a potential plaintiff it is equally true that the fact that something goes wrong does not necessarily imply negligence.

"It is not every slip or mistake which imports negligence. . . . In surgical operations there are inevitably risks."

These words were used in the judgment in Roe *v*. Minister of Health (1954). Two men in 1947 were paralysed by Nupercaine spinal anæsthetics. As was common practice, the ampoules had been stored in phenol solution, which entered through invisible cracks. No negligence was found because "in 1947 the general run of competent anæsthetists did not appreciate the risk". Once it was established the position changed, because an avoidable factor was identified and to ignore it in the future could provide evidence of negligence. Successful defence must establish that treatment was in accordance with general and approved practice. The judgment in this case, as in Rex *v*. Bateman (1925), made it clear that the law does not require the highest standards of practice but

". . . a fair and reasonable standard of care and competence. If the patient's death has been caused by the defendant's indolence or careless- ness, it will not avail to show that he had sufficient knowledge; nor will it avail to prove that he was diligent in attendance if the patient had been killed by his gross ignorance and unskilfulness."

The doctor in this case successfully appealed when convicted of manslaughter after a terrible obstetric tragedy. Under chloroform anæsthesia which he himself administered he failed to deliver with forceps, performed version, and extracted with great difficulty a stillborn infant. In removing the placenta manually he also removed most of the uterus, ruptured the bladder, damaged the colon and tore the rectum. The patient died. This case illustrated the narrow line which divides negligence in civil law from its counterpart in the criminal code. Lord Hewart stated that:

"To support an indictment for manslaughter the prosecution must prove the matters necessary to establish civil liability (except pecuniary loss) and, in addition, must satisfy the jury that the negligence or incom- petence of the accused went beyond a mere matter of compensation and showed such disregard for the life and safety of others as to amount to a crime against the State and conduct deserving punishment."

In summary, the five guiding principles emphasize the importance of medical care which provides the maximum safety for the patient and reduces to a minimum the chance of unhappy conflict. Thoughts of legal safety must not be allowed to influence professional judgment in patient care but a wider appreciation of how to avoid disputes should benefit both patients and doctors. An American lawyer, Morris L. Ernst (1963), stated:

"Our society is not coming to grips with the social impact of suits for malpractice."

He referred to the difficulty which often existed in appraising the fine line between error and negligence, and deplored the fact that in America doctors involved in litigation had to depend on officials in insurance companies and their lawyers to handle claims. In an attempt to improve the situation medical associations in some counties, with the approval of the State Bar, established plaintiff panels, which consist of doctors selected for the purpose of examining a plaintiff alleging malpractice (Hassard, 1963). In the first 250 claims a physician member of the panel went to court on 30 occasions to give evidence *in support of the plaintiff*. In this way public relations were improved and good will established. As they gained in stature these panels helped avert the filing of unjustified claims but when injury could be attributed to negligence they endeavoured with success to secure settlement on reasonable terms out of court. Only 19 of 250 claims in New Hampshire ultimately came to court and in 17 of these the defendant doctor won his case (Sulloway, 1963). This system was created to meet a need catered for in Britain and the Commonwealth by the several medical organizations offering protection to members of the medical and dental professions. In spite of them there are doctors who, for reasons known only to themselves, become involved personally with plaintiffs or their lawyers when charges alleging negligence are made. They sometimes prejudice their defence by inexperience and involve themselves unnecessarily in heavy expenses.

Certain problems common in obstetrical and gynæcological practice have legal implications which are now considered.

Sterilization

The desire of a healthy but broken-hearted woman to have another baby after she has been sterilized is one of the tragedies of practice. This aspect of a simple operation with dangerous medicolegal implications is sometimes forgotten. Circumstances can alter

quickly and change a woman's feelings. The death of a child, or a second marriage, can convert the peace conferred by tubal ligation into bitter resentment. The younger the woman the greater the danger and the more urgent the need to consider other contraceptive methods (Chapter 7). The operation should never be performed without the most careful assessment of all aspects of the case even when there are strong medical reasons to justify it, and much more so when these do not exist. Both partners should give written consent, confirming that they are aware of the implications of the procedure. The written approval of a colleague is a further wise precaution but even so there can be legal difficulties.

In Bravery v. Bravery (1954) divorce proceedings were taken on the ground of cruelty arising from the sterilization of a husband. The case was lost because the Court of Appeal found there had been at least a measure of consent but Lord Justice Denning in a dissenting judgment suggested that the operation of sterilization, even with consent but in the absence of medical reasons to justify it, might amount to unlawful assault similar to procuring an abortion. All three judges were unanimously of the opinion that a husband submitting to an apparently unnecessary sterilization would be guilty of a grave offence amounting to cruelty if he did not get his wife's consent prior to operation and if her health were injured because of it.

A gynæcologist performed a hysterectomy on a middle-aged woman. When the husband received the account he repudiated liability on the grounds that a sterilizing operation had been performed without his consent.

The position is that a married woman can consent to any operation which is advised in the interest of her life and health with no legal obligation on the doctor to obtain the husband's consent. Nonetheless it is prudent for him to do so and particularly before any operation which will make a woman sterile.

Consent

There are rare occasions when it may be impossible to obtain consent from either partner, as in emergencies such as a patient in coma. Permission may even be refused as in the following case.

Early in the war an officer's wife with her 5-year-old daughter and a nurse were on a ship which was torpedoed. The child was drowned. During the invasion of Europe the mother was admitted to hospital

bleeding from a major degree of placenta prævia with an associated transverse lie. She refused consent for section because she had promised her husband before he went to France that she would have no operation without his permission. When all attempts to change her attitude failed a technical assault was committed by administering a sedative prior to operating. When the mother wakened to find a baby in her arms she was grateful, as was her husband later.

In the unlikely event of a legal dispute in such a case the attitude a court would be likely to take was made clear in Rex *v.* Bourne (1939):

". . . the doctor is not only entitled, but it is his duty, to perform the operation with a view to saving her life."

Difficulties can arise in relation to consent for operation upon minors. In English law there is no rigid rule that renders a minor incapable of giving this but parental consent should also be obtained where possible. Life or health of a minor, whatever age, must not be jeopardized by waiting for parental consent, but except in emergency this should be obtained before operating on a patient under the age of 16. Opinion differs on whether this is necessary in a minor of 16 who is capable of appreciating what is proposed. There is no direct authority on whether consent of a minor aged 16–21 is sufficient. The rule of Common Law is that consent must be freely given without force, fear or fraud, and by a person who is able to form a reasonable opinion on the issues involved. For some purposes of civil law a person under 21 is under a disability whatever his age, but in so far as criminal responsibility is concerned a child of 8 and upwards may be, and one of 14 is, responsible for his crimes. Consent given by a child under 16 years of age does not constitute a defence against unlawful carnal knowledge. It would seem therefore that there is a distinction between those under 16 and those over. By Section 5(2) of the Mental Health Act, 1959, the wishes of a patient of 16 shall override those of his parents or guardian on "informal admission" to hospital. This implies that minors of 16 and upwards are expected to decide for themselves in relation to investigation and treatment under the Mental Health Act. It would seem reasonable therefore that this is a statement of what would be supported elsewhere in law. The National Health Service Regulations, 1954, give all persons not under 16 years of age and not physically and mentally incapable of doing so, the right to choose their own general medical practitioner and by implication to consent to procedures by him. In the same way, anyone not under 16 makes

his own application for dental treatment and signs the form of completion. These facts suggest that the effective age of choice is 16.

The corollary to this is that *a surgeon would be unwise to assume that the consent of the parent or guardian of a minor of 16 or over is equivalent to the minor's consent*. This point is sometimes overlooked. It appears that the consent of a minor aged 16–21 to whom the implications of an operation have been explained is all that is required, but it would obviously be wise when possible to obtain the consent of the parent or guardian as well. If there is conflict between the two, then providing treatment is essential the consent of the minor should be adequate in law.

Difficulty arises when dealing with a minor under the age of 16 and consent is withheld by parent or guardian, as when permission is refused for a blood transfusion considered necessary to save life. A letter from the Ministry of Health in 1962 to Regional Hospital Boards is relevant and ends as follows:

"Boards will be generally aware that in the past problems of this kind have been resolved by the doctor deciding his course of action by the dictates of his individual professional conscience. When advice has been sought it has been given on the lines that if the doctor gets the written supporting opinion from a colleague that the patient's life is in danger if operation or transfusion is withheld and gets an acknowledgement (preferably in writing) from the parent or guardian that he refuses consent despite the explanation of the danger given to him by the doctor, he runs little risk in a court of law if he acts with due professional competence and according to his own professional conscience."

Risks inherent in obtaining consent are discussed by Morris (1963) in a review of American medico-legal practice. He referred to the difficult problem of discussing operative risks, as for example the danger to the recurrent laryngeal nerve in thyroidectomy or the sterilizing effect of certain surgical procedures in both male and female. Even with this same operation the advice given will vary with different patients according to their reaction. For therapeutic reasons it may be wise not to disclose risks, but it is then the more important that the record should show clearly why the patient was not informed. As dangers increase so does the duty to warn the patient or relative and the need to record that this has been done. If hazards are very great the probability is that the procedure is not generally accepted practice and comes into the realm of experimentation. This requires the informed consent of the patient after which a bad result would come as less of a shock and the patient would be less likely to seek legal redress.

Operating on the Wrong Patient

An operation is merely an important episode in the recovery from illness. The surgeon who accepts this view will talk with, examine, and assess patients himself before he operates. This reduces the chance of making mistakes in the theatre. Altering the order on the operating list once a session begins increases the possibility of mistakes being made. A brief summary of the details of patients and the operations proposed displayed in the scrub-up room refreshes the surgeon's mind and decreases the chance of error.

Missing Swabs

Litigation arising from retained swabs or instruments is increasing in Britain. One organization responsible for professional defence handled 20 cases in 1959 and 38 in 1962. To leave a swab or instrument in the body of a patient is *prima facie* evidence of negligence, but the question of whether failure by a surgeon to remove all swabs, instruments, tubes or other paraphernalia constitutes lack of reasonable care must be decided on the evidence of each particular case. He is not entitled to rely solely on the theatre sister's swab and instrument count, although he should ask for this, but must take reasonable precautions himself. At the end of the operation he is obliged to make such search as is in his opinion necessary, providing that it is compatible with the welfare of the patient. Factors which predispose to inaccurate counts and leaving swabs or instruments in the body are:

1. Too much emphasis on operating speed. This may be essential in emergency but under other circumstances can be dangerous.
2. Lists which are too long. This may mean inadequate cleaning of theatres between cases, and swabs can get mixed when there is not time for the necessary counts. Fatigue can affect both surgical and nursing staff.
3. Using many small swabs when fewer larger ones would be safer as, for example, one Macfarlane roll during Cæsarean section (Chapter 1).
4. Relative inexperience of surgeon or nurse. A nurse may feel she has not the necessary authority to insist on effective swab control and this causes particular difficulty when surgeons and nursing staff are strangers. Team work is essential for good results.

14*

5. Changing teams during the course of an operation.
6. Removing swabs or instruments attached to specimens during an operation.

General Medical Council

This body published in 1963 guidance for doctors entitled "Functions, Procedure and Disciplinary Jurisdiction". It explains the constitution of the Council and the procedure it adopts in disciplinary cases. A section is headed "Notes on Certain Professional Offences" in which these are discussed in detail. A doctor knows that certain actions could result in the Disciplinary Committee finding him guilty of infamous conduct in a professional respect. The more important reasons for which this severe discipline can be enforced are summarized by the six A's. They are:

1. Abortion—criminally induced.
2. Adultery with a patient.
3. Addiction to drugs.
4. Alcoholism—interfering with professional standards.
5. Association with unqualified practitioners.
6. Advertising.

Several points are worthy of emphasis in relation to three of the above.

Abortion

The legal position in Britain is based on Sections 58 and 59 of the Offences Against the Person Act, 1861, and Section 1 of the Infant Life (Preservation) Act, 1929. The latter states:

"Any person who, with intent to destroy the life of a child capable of being born alive, by any wilful act causes the child to die before it has an existence independent of its mother, shall be guilty of felony, to wit of child destruction, and shall be liable on conviction thereof on indictment to imprisonment for life; *provided that no person shall be found guilty of an offence under this section unless it is proved that the act which caused the death of the child was not done in good faith for the purpose only of preserving the life of the mother.*"

It follows from the important judgment given in Rex *v.* Bourne (1939) that when the decision is taken to terminate a pregnancy *the act of doing so will be criminal or innocent according to the intention.* The question of whether termination of pregnancy is the correct course to adopt must depend on the circumstances of the case and

their assessment by a specialist, and a second opinion agreeing with the first is obviously desirable. In the event of dispute there would be no criminal charge to answer if it could be established that interference was in good faith for the purpose only of preserving the life of the mother. Under Section 58 of the Offences Against the Person Act the burden of proving that the operation was not done in good faith rests on the Crown and if the jury decide that proof is not established the accused is entitled to a verdict of acquittal. Further clarification of the Act was given in the Rex *v.* Bourne judgment, when it was stated that:

"The words 'preserving the life of the mother' must be construed in a reasonable sense. They are not limited to the case of saving the mother from violent death; they include the case where continuation of the pregnancy would make her a physical or mental wreck. . . . Where the doctor anticipates, basing his opinion on the experience of the profession, that the child cannot be delivered without the death of the mother it is obvious that the sooner the operation is performed the better. . . . In such a case the doctor is not only entitled, but it is his duty to perform the operation with a view to saving her life. . . . If a case arose where the life of the woman could be saved by performing the operation and the doctor refused to perform it because of his religious opinions and the woman died, he would be in grave peril of being brought before this Court on a charge of manslaughter by negligence."

In English law there is no provision for procuring an abortion simply because of the possibility of fœtal deformity. This is relevant to problems which arise when a woman contracts a virus infection, receives radiation, or is given drugs in the early stages of pregnancy. In all such cases the question of termination must be decided upon the mother's response and not on the estimated fœtal risks.

Adultery

A recent decision of the Disciplinary Committee, supported on appeal to the Privy Council, found a doctor guilty of "infamous conduct in a professional respect" and erased his name from the register when he had an amorous, although not adulterous, relationship with a patient involving sexual intercourse. There had been no element of seduction nor had matrimony been intended and the association ceased long before the charge was made. In giving judgment on appeal Lord Upjohn stated:

"A doctor must never permit his professional relationship with a patient to deteriorate into an association which would be described by a responsible medical opinion as improper. . . . Sexual intercourse with a patient has always been regarded as a most serious breach of the proper

relationship between doctor and patient and their Lordships do not see how the finding of the Committee, on the facts of this case, that the appellant was guilty of infamous conduct in a professional respect can be successfully challenged before their Lordships."

Advertising

Notice should be taken of a recent development which could lead to trouble. Local directories are published in many parts of the country and canvassers sometimes invite medical and dental practitioners to subscribe for copies at a charge in excess of the normal cost but to include in the classified section the insertion of the doctor's name, qualifications and surgery address. Any such publication dependent upon the payment of a fee would be a breach of professional ethics and could be construed as advertising. Some publishers, aware of the ethical limitations relating to the insertion of doctors' names in directories, have co-operated with the professional associations on these matters as there is no objection to an entry in a local directory of a practitioner's name and address provided the list is open to all doctors in that area and no charge is made for the entry.

The Limitation Act, 1963

This came into force on the 31st of July, 1963. It provides for extension in certain cases of the 3-year time limit applicable to action of negligence. A plaintiff may now, with leave of the Court, bring an action for damages for personal injuries, although the 3-year limit imposed by section 2 (1) of the Limitation Act, 1939, has expired, if it can be proved that the material facts relating to the cause of action were outside the knowledge (actual or constructive) of the plaintiff until a date which was either after the end of the 3-year period, or was not earlier than 12 months before the end of that period. In either case, the facts must be known to the plaintiff on a date not earlier than 12 months before the proceedings commenced. The increased time interval now allowed gives further emphasis to the need for accurate records which could prove decisive in defence.

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VAGINAL ABSENCE OR ATRESIA

A NEW OPERATION

Congenital absence of the vagina is uncommon, but postoperative stenoses and strictures are a not infrequent cause of dyspareunia and unhappiness. Attempts to create an artificial vagina have been based on either the utilization of a loop of intestine, with all its disadvantages and dangers, or lining with skin graft a cavity prepared by separating the urethra and rectum.

The technique devised by the late Sir Archibald McIndoe and Sir Charles Read in 1936 was widely adopted. It consists of leaving a plastic mould covered with split skin graft of 20 cm. $\times$ 10 cm. in place for 6 months. Counsellor (1948) reported from the Mayo Clinic a perfect result in 52 of 76 patients, and a fair result in the remainder. Simmons (1959) published the results of 101 operations performed at Chelsea Hospital for Women, chiefly by Read and McIndoe, with success in 97. Four patients developed recto-vaginal fistulæ. The result was unsatisfactory, however, in 6 of 32 who were examined a year or more later. If neither regular intercourse nor the insertion of dilators keeps the vagina open it contracts and shortens.

Nonetheless, the Read–McIndoe operation was a great advance on former techniques but it has three disadvantages. There is a small risk of even an experienced surgeon damaging rectum or urethra, the thigh area from which the graft is cut is left permanently scarred and keloid changes can be unsightly, and a plastic surgeon is required to prepare an adequate graft. The author remembers the applause which greeted McIndoe as he displayed the second of two perfect grafts cut without blemish and with apparent consumate ease when he first demonstrated the operation with Read on two consecutive patients at Chelsea Hospital for Women. *Ars est celare artem.*

Williams (1964) devised a brilliantly simple technique which has none of these disadvantages. It keeps the patient in hospital only 10 days, creates a functioning vagina from skin richly endowed with nerve endings designed to respond to sexual stimulation, and does not require the assistance of a plastic surgeon.

The labia majora are separated to display the vulval area as shown in Fig. 66. A cresentic incision is made on the inner aspect of the labia (Fig. 67) 5 cm. from the midline and the medial edges are sutured from behind forwards to create an adequate elongated space capable of accommodating a large mould or glass dilator (Figs. 68 and 69). The surrounding tissues and skin edges are finally sutured in layers (Fig. 70).

Designed primarily for patients with congenital absence of the vagina, it can be adapted to remedy stenosis or shortening as seen sometimes after colporrhaphy or Wertheim hysterectomy. The contribution this new technique can make is well illustrated by the following case report:

Mrs. H. K. was 28 and had failed to consummate her marriage. The reason for this was that she had been born with congenital abnormalities including a cloaca with a recto-vaginal fistula. In infancy she was treated by colostomy and later a pull-through operation was performed which fortunately not only closed the fistula but gave her complete rectal continence.

Menstruation commenced at the age of 13, the fluid escaping through a narrow fistulous track. It was obvious that any attempt to reconstruct a vagina by conventional techniques was fraught with the danger of

FIG. 66

FIG. 67

FIG. 68

Fig. 69

Fig. 70

interfering with the excellent result of the earlier bowel operation. For this reason this particular patient was considered an ideal subject for the new technique and was referred to Mr. Williams for his opinion. He agreed to demonstrate the operation at Oxford on 24th July 1965 and obtained an excellent result. This was the eighth patient treated by the new method.

Results

The operation was performed on 5 patients for congenital absence of the vagina, on one because of congenital anomalies referred to in the above case history, on one because of severe stenosis following the repair of prolapse and on one because of sexual incapacity after a Wertheim hysterectomy. All these patients had an adequate vagina after operation and from the point of view of function the results to date have been excellent.

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New Classification of Uterine Cancer in International Report

The Report, first published in 1937 from Stockholm, is now under the patronage of the International Federation of Gynecology and Obstetrics. The 13th Volume (1964) includes for the first time reference to carcinoma of the vagina. The Editorial Committee plans to publish future Reports at 3-yearly intervals to coincide with the International Congresses of Gynæcology and Obstetrics.

Classification

New classifications adopted by the International Federation at its meeting in Vienna in 1961 came into operation on January 1st, 1962. They are:

1. *Carcinoma of the Cervix*

    This includes all patients whose primary tumour is in the cervix irrespective of its histological type. It also includes those patients with advanced pelvic cancer in whom it is clinically impossible to determine the site of origin of the growth, provided the cervix is invaded and the tumour histologically is epidermal.

2. *Carcinoma of the Corpus*

    Patients are in this group when the primary growth is in the body of the uterus. It also includes those in whom carcinoma of the corpus develops more than 5 years after ovaries have been removed for ovarian carcinoma, provided there is no evidence of recurrence of the ovarian lesion.

The following terms used in previous Reports are no longer included: carcinoma corporis et endocervicis; carcinoma vaginæ et cervicis; carcinoma uteri et ovariæ; carcinoma pelvis.

A corollary to the omission of carcinoma corporis et endo-cervicis is that patients previously classified under this heading must now be included in either the cervix or corpus groups. For example, a carcinoma arising in the cervix but extending to involve the body

of the uterus will be classified as Stage 1b carcinoma of the cervix. Similarly, a carcinoma thought to be commencing in the corpus but extending to involve the cervix would be classified as carcinoma of corpus Stage 2. It can be difficult and even impossible to decide whether a carcinoma arises in the endocervix or extends from the corpus. In its Handbook of Guidance on Registration of Gynæcological Cancer the Committee admits that surgical staging is desirable but states that clinical and surgical stagings must be kept separate. The former is required for registration in the Annual Report because the only institutions in which the more accurate surgical staging could be used would be those employing operative techniques. Most patients are treated by radiotherapy in the institutions providing data for the Report. For this reason, clinical staging is adopted in spite of its defects.

If examination and fractional curettage leave doubt as to the origin of the tumour it is recommended that it should be allocated to carcinoma of corpus if it is an adenocarcinoma and to carcinoma of cervix if squamous.

The method of registration was revised and a new table introduced to make possible a more accurate analysis of cases of uterine cancer and their response to treatment. It includes details on pathology, age, associated malignant conditions, and the response to treatment of recurrent tumours. Relevant information is recorded on punch cards for machine analysis. The new system commenced in January, 1962. Problem cases will arise with difficulty of classification and collaborators are invited to send details to the Editorial Office at Radiumhemmet, Stockholm 60, Sweden, from which necessary advice will be given.

The Handbook advises as follows on preparation of the annual tables for submission to the central office:

1. *Classification*

   This means the group to which the growth belongs because of its site of origin; cervix or corpus. *Histological confirmation is essential.*

2. *Staging*

   This is synonymous with "stage grouping" and refers to the extent or spread from the primary tumour as assessed on *clinical* examination.

Guidance is given on what constitutes clinical examination for the purpose of staging. It includes curettage, cystoscopy, biopsy, and

conization or amputation of the cervix. Micro-invasion diagnosed in this way is classified as Stage 1a carcinoma of cervix. It is inevitable that a lesion diagnosed clinically as Stage 0 and treated by simple hysterectomy will sometimes be found by the pathologist to be associated with micro-invasion. The original preoperative diagnosis should not be altered. Patients in this category would be registered under Stage 0 even although further evidence proved the diagnosis to be Stage 1a. This is in accordance with the principle by which the staging of invasive carcinoma is not altered because of operative findings. For example, if a Stage 1 carcinoma of cervix is found at operation to have gland involvement it remains as Stage 1. *Clinical staging must under no circumstances be altered* even if operation or autopsy reveals that a mistake has been made.

Whereas X-rays of the lung or skeleton are considered part of the clinical examination permitting the appropriate staging should there be metastases, more complicated radiological procedures involving arteriograms, venograms and even pyelography are excluded because they are not available in all collaborating institutions.

Much can be said in favour of the general adoption of the tables used for the International Report even if institutions are not submitting these for inclusion. It would make it easier for them to collaborate in the future and in the meantime facilitates comparison between results. The potential value both to contributor and reader of analyses of a massive clinical material cannot be overemphasized, but success depends on initial accurate detailed recording. The development of a system which makes records available on request, and reliable when analysed, is of prime importance, is often ignored, but is essential for a high standard of work. Readers interested in historical details of the Annual Report are referred to an excellent summary by McGarrity (1963).

The amended staging adopted in Vienna in 1961 is as follows:

Preinvasive Carcinoma of the Cervix (Stage 0—carcinoma-*in-situ*— intra-epithelial carcinoma)

Patients in this group are *not* included in statistics dealing with carcinoma of the cervix. If hysterectomy is performed and invasion is subsequently diagnosed by the pathologist the case remains classified as Stage 0 but an explanatory note is necessary for separate recording to make these patients available for further study.

This important lesion is discussed in detail in Chapter 8, but it is *not* cancer in the usual meaning of the word. By definition it

does not metastasize and once removed *it will not recur.* It is often multi-focal in origin and may be associated with adjacent invasive carcinoma. Like an area of open cast mining in the immediate vicinity of deep mines the presence of the one neither confirms nor disproves the presence of the other. When multi-focal one lesion can be removed while others are overlooked.

Uterine Cancer

(*a*) *Carcinoma of the Cervix Uteri*

> *Stage* 1. Refers to invasive carcinoma confined to the cervix, or originating in the cervix and extending upwards to involve the body of the uterus. It is sub-divided into two groups:
> *Stage* 1*a*. Early stromal invasion, including micro-invasive carcinoma *providing this is diagnosed from biopsy specimens before treatment is given.* Micro-invasion detected on histological examination after removal of a uterus with the preoperative diagnosis of carcinoma-*in-situ* should not be included in the statistics of invasive carcinoma.
> *Stage* 1*b*. All other cases of Stage 1 growth. This includes extension to the corpus.

> *Stage* 2. The carcinoma extends beyond the cervix but has not reached the lateral pelvic wall. This is sub-divided into two groups:
> *Stage* 2*a*. The carcinoma has spread into the para-metrium.
> *Stage* 2*b*. The carcinoma involves the vagina but not the lower third.

> *Stage* 3. The carcinoma has extended to the pelvic wall. On rectal examination there is no cancer-free space between the tumour and the pelvic wall.
> The tumour involves the lower third of the vagina.
> *Note.* When a growth is fixed to the pelvic wall by a short indurated but not nodular parametrium the case should be allotted to Stage 2. This is on the basis that it is better to understage than overstage in a case of doubt and with these physical signs parametrial induration may well be inflammatory. If the parametrium is nodular the case should be allotted to Stage 3.

Stage 4. The carcinoma has extended beyond the true pelvis or has involved the bladder or rectal mucosa.

> *Note.* Bullous œdema *per se* does not justify allocation of a case to Stage 4. Digital palpation during cystoscopy will show whether ridges and furrows are adherent to an underlying tumour, but in the Handbook it is recommended that these cases should be included under Stage 4 only if invasion is proved by biopsy.

Cases of advanced pelvic carcinoma in which it is clinically impossible to determine the exact site of origin of the growth should be included as carcinoma of cervix Stage 4 providing the cervix is invaded and the tumour is of the squamous cell type.

(*b*) *Carcinoma of the Corpus Uteri*

Stage 0. Histological findings suspicious of carcinoma but not definite.

Stage 1. The carcinoma is confined to the corpus.

Stage 2. The carcinoma has spread to the cervix.

Stage 3. The carcinoma extends beyond the uterus but not outside the true pelvis; for example, tubes, ovaries, or pelvic glands are involved.

Stage 4. The carcinoma extends outside the true pelvis or involves the bladder or rectum.

Note. When it is difficult to decide whether a carcinoma is endocervical or a carcinoma of the corpus and endocervix it should be classified as carcinoma of the corpus if it is an adenocarcinoma and carcinoma of the cervix if a squamous cell tumour.

Circumcision

The relative freedom of the Jewish cervix from carcinoma has been extensively documented by Kennaway (1948), Weiner *et al.* (1951), Hochman *et al.* (1955), Israel (1955) and many others. Factors such as racial susceptibility, the Mosaic code of cleanliness and male circumcision have all been considered as responsible or contributory factors. Circumcision has received more attention in recent years, but the type of operation may be important and to classify males into circumcised and uncircumcised could be misleading without further information on the extent of foreskin removal. Wynder and Licklider (1960) defined four variations resulting in complete exposure of the sulcus at one extreme and a covered glans at the other. Penile cleanliness can be directly affected by the proportion of prepuce retained and if smegma is carcinogenic, and further evidence is required on this point, its action on both the glans and the cervix would be influenced by the extent to which it is retained beneath an incompletely removed prepuce, or removed by attention to hygiene.

The World Health Organization Committee on Cancer Prevention in Geneva (1963) accepted that "there is epidemiological evidence regarding the association of carcinoma of the uterine cervix with early marriage, absence of circumcision in the male partner, and several other factors". Wynder (1955) and Rao *et al.* (1959) reported a lower incidence of cervical cancer in Muslim women, whose husbands are circumcised, than in the Hindu women, whose husbands are not. Eser (1964) stated that in Turkey 99 % of women are Muslim and 96 % of males are fully circumcised. An extensive survey led to the conclusion that circumcision performed in the fifth or sixth year of life reduces the incidence of penile cancer, but has little effect on carcinoma of the cervix. The incidence of this disease in Turkish women is approximately 12 % of all cancers, a figure comparable to that found among Western women and in the non-Muslim and non-Jewish population of Turkey. Turkish women are usually younger than Jewesses when they marry and bear children. The fact that Parsee women seldom develop cervical cancer although their

husbands are uncircumcised appears to challenge the concept of circumcision being prophylactic, but Wynder discussing this point emphasized the careful attention of Parsee males to personal hygiene. In Fiji there are two groups living under comparable conditions. Fijians are circumcised and their wives seldom develop cancer of the cervix, but Indians whose husbands are uncircumcised do.

Heins *et al.* (1958) claimed that carcinoma of the penis has not been reported in a male properly circumcised as an infant. The possible carcinogenic effect of smegma has been studied. Equine smegma applied to the skin of mice has induced epitheliomatous changes (Plaut and Kohn-Speyer, 1947) and human smegma applied to the mouse cervix has been followed by carcinoma as described by Heins *et al.* (1958) and Pratt-Thomas *et al.* (1956). The evidence is suggestive rather than conclusive. Mycobacterium smegmatis may conceivably produce a carcinogen, but accumulated smegma indicates poor personal hygiene and this may be the important factor.

On grounds of cleanliness obstetricians and pædiatricians should instruct parents on the importance of penile hygiene if the infant is not circumcised. If they are unwilling or unable to attend to this matter it is an argument in favour of circumcision. While it is true that there is no evidence that circumcision reduces the relatively low incidence of cervical cancer associated with high hygienic standards it is also true that effective circumcision makes it easier for these standards to be maintained.

"To be or not to be?" That is the question which worries many parents wondering whether their son should be circumcised or not. Shakespeare also provides the corollary, "twere well it were done quickly", or in other words if a mature healthy infant needs circumcision it is better done during the first week of life. Many doctors recall their early operative experience as house surgeons circumcising with bone forceps unfortunate infants and children. Sometimes too much was removed and sometimes too little. Attempts to control bleeding produced ugly clumps of ligatured tissue and left memories that are the basis of many horror stories associated with infant circumcision.

Some obstetricians do not examine the infants they deliver nor give advice on whether circumcision is necessary. Some pædiatricians are strongly opposed to "interfering with nature", and remember stories, possibly true, of mutilated organs following circumcision by unskilled surgeons, but as an alternative they do not advise the

mother on the genital hygiene of the infant. This *laissez-faire* attitude allows mothers to leave hospital without guidance on these matters and infants are referred back to Casualty for circumcision months later, when it is more difficult for both child and parents.

Use of the Gomco clamp* (Fig. 71 makes circumcision a neat, bloodless and relatively atraumatic procedure. A larger clamp is applicable for older males. Chloral hydrate grains 1–3, according to weight, given 30 minutes before operation is all that is required for analgesia in the first 7–14 days of life. A glucose drink soothes the infant if awake. With aseptic technique the prepuce is gently freed from the glans and after a dorsal slit when necessary is retracted to expose the sulcus. Smegma is removed by a moist swab. Three pairs of mosquito forceps are applied to the muco-cutaneous junction at the meatus and the glans protector (Fig. 72) is inserted. The clamp is assembled so that redundant prepuce under slight traction is compressed at its base by the instrument when the screw is tightened to its maximum. Redundant tissue is excised by cutting with a scalpel on to the meatal protector and compression is maintained for 4 minutes. When the clamp is removed the result is as shown in Fig. 73, with no bleeding, no sutures and no raw area. A Vaseline gauze dressing protects the glans for the first 24 hours.
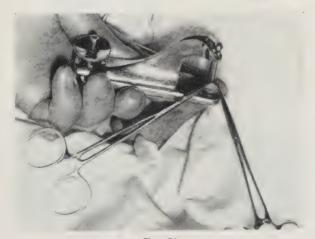
Fig. 71

* This is manufactured by the Gomco Surgical Manufacturing Corporation, Buffalo, U.S.A., and can be obtained from Surgicon Ltd., Wakefield Road, Brighouse, Yorks.

Fig. 72

Fig. 73

Under no circumstances should the diathermy be used in infant circumcision, and with the technique described above it is unnecessary. The distress caused by destruction of the glans secondary to diathermy burns is likely to influence adversely the whole life of a male, and damages awarded against the doctor because of his negligence in the use of diathermy for circumcision have on occasions been very heavy.

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